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CARCINOMA OF THE HEAD OF THE PANCREAS

The Effects of Obstruction on the Ductal and Acinar Systems

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THE LITERATURE on the pancreas abounds with experimental data regarding the effects of ligation of the duct on the gross and histologic structures of that organ as well as the physiologic alterations in the organism incident to this procedure. However, to our knowledge a separate investigation has not been made of the effects of obstructing carcinoma of the head of the pancreas on the ductal and acinar systems in particular and on the organ in general. The mechanism of the obstruction of the ductal system in cases of carcinoma of the head of the pancreas is obviously quite different from that encountered in experimental ligation. In the former the process is insidious; in the latter, sudden. While obstruction, the end result, is the same in each instance, the pathologic and even the physiologic effects may be at variance.

For a complete review of this entire subject up to 1920 the reader is referred to the excellent paper by Barron,[1] who concluded that (1) obstruction of the pancreatic duct leads to advanced atrophy and fibrosis of the pancreas and that (2) hyperplasia of the ducts may occur as a regenerative attempt in cases of injured pancreatic tissue. Except for the work of Kodama,[2] the literature makes little mention of retention cysts in the experimental animal; these cysts are seen occasionally in cases of obstruction of the pancreatic ducts of human beings. Reference should be made here to the marked variations encountered in the normal structure of the pancreas. Oertel and

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1. Barron, M.: Surg., Gynec. & Obst. **31**:437, 1920.
2. Kodama, R.: Fukuoka acta med. **28**:35, 1935.

Anderson,[3] as well as Reitmann,[4] described the following specific variations in acini: (1) some cells enlarged, with pyknotic nuclei, and others showing simple atrophy; (2) simultaneously, regenerative phenomena exhibited by enlarged acini, the cells of which contain normal nuclei; 3) degenerative and atrophic changes in acinar cells, and (4) cellular and tubular formation of the pancreatic parenchyma.

Collapse of acini, changes in the epithelial lining, luminal debris and regenerative and degenerative changes in acinar cells are among the more important variations in normal tissue. Admittedly, diseases which affect parts of the body that are widely remote from the pancreas may enhance some of these changes.

Since primary carcinoma is the most important lesion of the pancreas, much has been written on the pathologic features of this disease, but only a few papers include descriptions of changes occurring in the ducts and acini as a result of carcinomatous obstruction.[5]

Recently determinations of the concentration of the lipase in the serum have been employed to reflect diseased states of the pancreas. Comfort[6] found elevated levels less frequently in cases of carcinoma of the pancreas than in cases of pancreatitis.

Nothmann[7] reported interesting observations on increased concentrations of the alkaline phosphatase in the serum of dogs in which the pancreatic duct had been ligated. The subject, however, is chiefly of academic interest at present.

MATERIAL AND METHODS

Of 80 cases of carcinoma of the head of the pancreas, in which necropsy was performed at the Mayo Clinic during the period of 1936 through 1946, only 25 were found suitable for our study. These fulfilled the following criteria: 1. The gross specimens were reasonably intact, so that individual relationships between the ducts of Santorini and Wirsung, between the pancreatic ducts and the common bile duct, between the major and the minor papilla and between the pancreas and the duodenum were readily discerned before one proceeded with gross dissection and microscopic observation.

2. The lesion represented an intrapancreatic neoplasm and not merely an extraneous neoplasm encroaching on the organ.

3. Complete obstruction of the ductal system was apparent in the head or the neck of the organ or both, as determined by careful probing and sectioning in the region of the obstruction.

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3. Oertel, H., and Anderson, C. M.: Scientific Report, Royal Victoria Hospital, Montreal, 1916, series B, no. 1, p. 163.

4. Reitmann, K.: Ztschr. f. Heilk, **26**:1, 1905.

5. Grauer, F. W.: Arch. Int. Med. **63**:884, 1939.

6. Comfort, M. W., and Osterberg, A. E.: M. Clin. North America **24**:1137, 1940.

7. Nothmann, M. M.: Proc. Soc. Exper. Biol. & Med. **57**:15, 1944.

4. The entire pancreas and enough of the adjacent duodenum to identify the major and the minor papillae were available for study.

The cases of patients who had undergone surgical procedures beyond a palliative cholecystogastrostomy or a similar anastomosis were not included. A few clinical data were included, such as the concentrations of the serum amylase and lipase and the blood sugar when those had been determined. Changes noted in the islands of Langerhans will not be reported, since they are not within the scope of this investigation.

Gross anatomic studies included: tracing the duct of Wirsung both longitudinally and via cross sectioning; identifying the duct of Santorini when it was not wholly destroyed by neoplastic invasion, in order to study the possibility of its acting as a "safety valve" outlet for the obstructed chief duct; carefully probing the obstructed end to check for any remaining duct communicating with the duodenum; measuring the luminal circumference at the point of maximal dilatation of the duct and at a point 4.0 cm. from the tip of the tail (table 1); exploring each specimen for cysts and, if any were present, measuring their diameters; estimating the portion of the organ replaced by fat.

In order that the degree of dilatation of the obstructed ducts might be more fully appreciated, normal pancreatic ducts were carefully measured in a group of 10 selected specimens.

Microscopic observations were made of changes in the ducts, such as: squamatization, flattening or desquamation of the epithelial lining, and other degenerative phenomena; thinning of the wall of the duct; the degree of interlobular and intralobular fibrosis; acinous changes; the extent of fat necrosis, pancreatitis and calcification. In addition, a search was made for smaller cysts, which were classified.

Microscopic sections were taken across the duct at the point of maximal dilatation and at a point 4 cm. from the tip of the tail of the pancreas. In addition to this routine, sections taken from head, body and tail also were studied. The sections were fixed in formaldehyde solution (37 per cent) and stained with hematoxylin and eosin. Since most of the pathologic alterations exclusive of the neoplastic invasion were presumed to be primarily the result of atrophy, degeneration, replacement fibrosis and, to a lesser extent, inflammation, a plan of evaluation had to be made. It was thought most practicable to grade the severity of these changes on the basis of 1 to 4, grade 4 representing the most extensive change and grade 1 the least. When a change was not observed and the tissue appeared to be normal, the designation was zero. An evaluation was made of the severity of the changes in the head and the body of the pancreas as contrasted with the severity of the changes in the tail. In the latter region most of the sections were taken at a point approximately 4 cm. from the tip of the tail. In table 2 the cases are classified according to the severity of each pathologic alteration, graded again on the basis of 1 to 4. Here, also, cases which exhibited no change are grouped under zero.

RESULTS

In the 10 cases without carcinoma in which the ducts were found to be normal, the average inner circumference in the midportion of the head and that of the body, respectively, were 6.4 and 4.3 mm. The smallest measurements were 5.0 and 3.0 mm., respectively, while the largest were 9.0 and 5.0 mm.

Of the 25 patients having carcinoma of the head of the pancreas, who were selected for this study, 19 were men and 6 were women. The ages ranged from 43 to 89 years, the average being 61.8 years. In a few instances the growth had extended beyond the neck of the pancreas to include the proximal portion of the body.

In every case, obstruction of the chief and accessory ducts was complete, as determined by careful probing and dissecting of the ducts in the head to exclude the possibility that they were connected with the duodenum via either the minor or the major papilla. Indeed, the accessory duct was completely obliterated in every instance.

Before proceeding with dissection and measurement of the ducts, the organ and its relationships were evaluated as a whole.

The amount of tissue replaced by fat was roughly proportional to the degree of parenchymal atrophy exclusive of the neoplastic infiltration. Therefore, it appeared more practicable to estimate the degree of atrophy or of destruction of the gland in terms of fatty replacement, graded on the basis of 1 to 4, whereby grade 1 indicates that the amount of fat is just within detectable limits and grade 4 that the gland is completely replaced by fat.

In most instances the gland, no matter how atrophic it actually was, retained much of its original size as a fatty silhouette. Exceptions to this occurred in those cases in which the clinical histories disclosed that the patient had undergone a notable loss of weight and often emaciation. In such instances only a firm fibrous band, barely reminiscent of the pancreas, remained. Because of these variations, actual weights of the specimens were avoided, since they would tend to contradict the facts. The remaining pancreatic tissue was invariably firmer than normal tissue.

The grade of fatty replacement in each case is indicated in table 1. It is interesting to note that a rough correlation exists between the degree of fatty replacement and the degree of ductal dilatation.

In 13 cases fatty replacement was of grade 3 or more.

The chief pancreatic duct was exposed and traced longitudinally throughout its entire course. It was found that only 8 specimens (32 per cent) exemplified the so-called cylindric type of dilatation as shown in figure 1*a*, while in 16 others (64 per cent) the dilatation proved to be of the saccular type (fig. 1 *b*). The remaining dissection revealed a combination of the two, namely, cylindric in the body and saccular in the tail.

In each specimen, the midpoint of the area of maximal dilatation of the chief duct was selected, and its distance from the major papilla was carefully measured. The average distance, for all 25 cases, was 5.36 cm., while the extremes were 3.0 and 9.0 cm. (table 1). The

specimens which revealed the greatest distance from the major papilla to the point of maximal dilatation were almost invariably those in which the carcinoma was extensive, the head and neck of the gland usually being involved, while the reverse may be said for those specimens in which the distance was shorter. The striking dilatation of the duct in both body and tail in cases 15 and 24 represents the exception to the rule (table 1).

At the site of maximal dilatation the average inner circumference of the chief duct was 2.25 cm. The least dilatation was 0.9 cm. and

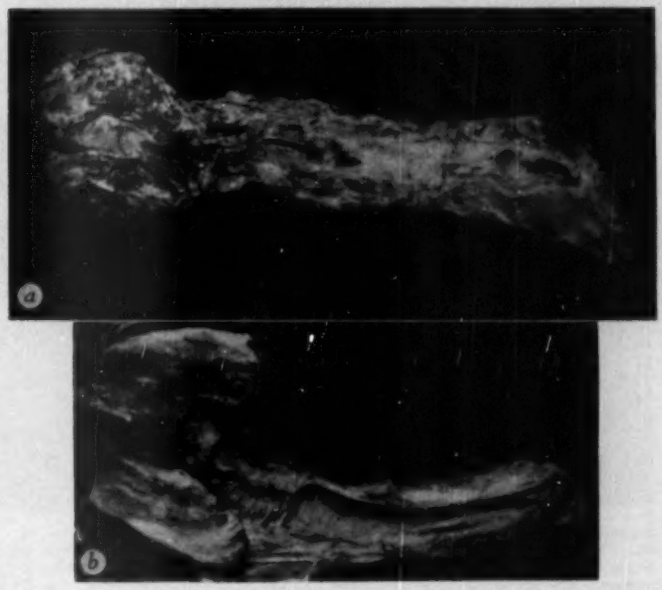

Fig. 1.—(*a*) Example of the less common cylindric type of dilatation of the duct of Wirsung. The neck and proximal end of the body of the pancreas have been invaded by carcinoma, so that dilatation of the duct is prevented in those areas. (*b*) Carcinoma of the head of the pancreas and saccular dilatation of the duct of Wirsung.

the greatest 3.8 cm. Measurements of the average distance showed that maximal dilatation occurred invariably in the proximal portion of the body, or just beyond the periphery of the carcinoma.

In estimating the degree of distention of the duct in the tail, an arbitrary point was selected, 4.0 cm. from the tip of the tail, with full realization that the variability of the length of the specimens altered the relative location of this site considerably. The average inner circumference of the duct at this point was 1.24 cm.; the smallest was

0.2 cm. (less than normal) and the largest 3.1 cm. In 1 specimen the duct was not found in this area, because of the presence of multiple cysts (case 18).

In 6 instances (cases 1, 2, 8, 13, 14 and 15) there was less than 5 mm. difference between the circumference at the site of maximal dilatation and that in the area 4 cm. from the tip of the tail.

TABLE 1.—*Data from Gross Examination*

Case	Age, Years	Sex	Dilatation *	Distance from Major Papilla to Site of Maximal Dilatation, Cm.	Circumference of Lumen of Duct of Wirsung: At Site of Maximal Dilatation, Cm.	Circumference of Lumen of Duct of Wirsung: At Point 4.0 Cm. from Tip of Tail, Cm.	Approximate No. of Cysts	Diameter of Largest Cyst, Cm.	Gross Fatty Replacement of Pancreas, Grade †
1	65	M	S	5.5	1.4	1.2	0	...	1
2	62	M	S	4.3	1.5	1.1	0	...	2
3	57	F	S	7.0	2.1	1.4	0	...	3
4	76	M	S & C	5.0	2.5	1.8	0	...	3
5	57	M	S	4.0	3.5	1.8	5	0.8	1
6	65	M	S	6.0	3.5	0.9	50+	0.7	1
7	43	M	S	4.5	1.5	0.6	0	...	0
8	68	M	S	7.0	1.2	0.5	0	...	2
9	51	M	S	5.0	1.3	0.2	5+	0.2	1
10	57	M	C	5.0	1.7	1.0	0	...	3
11	66	M	C	7.0	2.2	1.5	50+	0.2	3
12	77	M	C	5.0	2.0	1.1	0	...	3
13	53	M	C	7.5	1.5	1.4	0	...	2
14	58	F	C	3.0	0.9	0.8	0	...	0
15	71	M	S	7.0	2.5	2.1	50+	1.0	3
16	52	M	S	6.0	1.8	1.0	0	...	1
17	64	F	C	3.0	1.9	0.6	0	...	2
18	64	M	S	9.0	2.6	Multicystic	100+	9.0 by 5.0	3
19	48	M	C	5.7	1.9	1.1	0	...	3
20	56	F	S	4.5	1.6	1.1	1	1.0	2
21	60	F	S	3.0	2.8	1.5	0	...	3
22	62	F	S	5.3	2.5	0.8	0	...	3
23	56	M	S	4.5	2.0	1.3	0	...	3
24	62	M	S	3.0	3.0	2.5	0	...	3
25	62	M	C	5.0	2.5	1.0	0	...	3
Average	61.3	..	..	5.36	2.25	1.24	..	...	..

* S stands for saccular dilatation; C, for cylindric dilatation.
† The gross fatty replacement is graded on the basis of 1 to 4, in which 1 equals the least replacement and 4 the greatest. Zero indicates no change.

The findings in this series indicate that cystic changes of the ducts (cystic degeneration) are commoner in cases of pancreatic carcinoma than is generally supposed. Seven specimens (28 per cent) showed variable degrees of cystic change. The number of gross cysts throughout each specimen was estimated roughly as indicated in table 1, by gross serial sections. In case 20 the specimen contained a solitary retention cyst, which measured 1 cm. in diameter; on the other extreme was the specimen of case 18, which was estimated to contain more than 100 cysts, the largest of which measured 9 by 5 cm. (fig. 2). They con-

tained milky, slightly viscid fluid. In fact, in case 18 the pancreas had been transformed into one mass of cysts except for the persistent neoplasm in the head. The ductal system had been destroyed except for the dilated remaining segment located approximately 9 cm. from the head. It was impossible to say on gross examination whether or not these cysts were of the retention variety, since it was impossible to ascertain that they communicated with the residual ductal system.

In every instance the chief duct diminished rapidly in caliber as it entered the neoplastic portion and soon was completely obliterated.

ANALYSIS OF INDIVIDUAL PATHOLOGIC CHANGES

Secretion in the Ducts.—Secretion was present in sections of 17 specimens of tissue (68 per cent). It usually contained detritus admixed

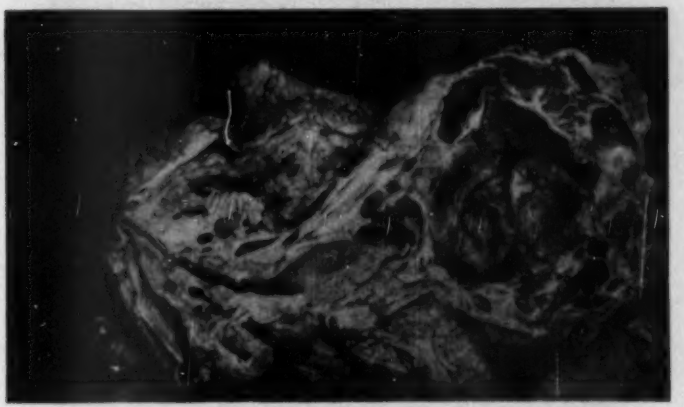

Fig. 2.—Portion of the head and body of the pancreas which has undergone multicystic change. The duct of Wirsung was completely obstructed in the head and dilated in the neck and body but was lost in the multicystic mass in the region of the tail.

with a few polymorphonuclear cells and some fibrin. Occasionally fine fibrin-like trabeculae were seen, suggesting inspissation. Much of the detritus was probably cellular and derived from sloughing or desquamation of the epithelial lining of the duct. The character of the secretion varied somewhat with the stage of degeneration of the duct. Little secretion was encountered in sections of the duct of Wirsung, but it may well have been washed out in the process of fixing and staining. The character of the retained secretion is well illustrated in figure 3*a*.

Flattening and Desquamation of the Epithelium of Ducts.—Flattening of the epithelium usually preceded desquamation or sloughing. Difficulty arose at this point in distinguishing actual sloughing of the

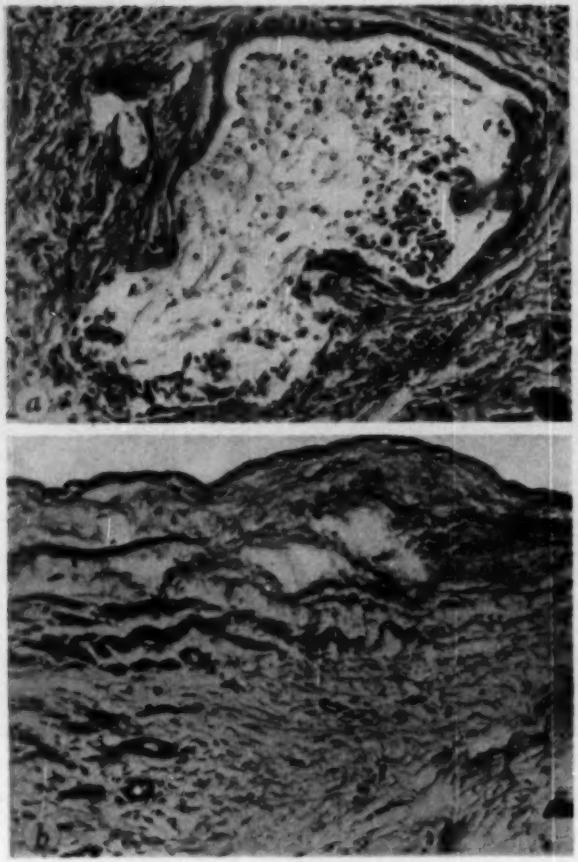

Fig. 3.—(*a*) Smaller excretory duct in various stages of degeneration. In the inspissated secretion are polymorphonuclear leukocytes, fibrin and desquamated cellular detritus. The cells forming the lining show many vesicular nuclei and are poorly outlined and flattened in some areas. Note the complete breakdown of the ductal wall in the lower portion. The remaining wall is thin, and many periductal lymphocytes are present. (Hematoxylin and eosin; × 160.) (*b*) Lining and wall of the duct of Wirsung which show the early effects of increased intraductal pressure. The epithelium has become compressed into a cuboidal type, and a few nuclei are compressed. Outlines of cells are indistinct, and the collagenous wall shows definite thinning. In the surrounding parenchyma the cells of the acini have been compressed into cords of atrophic cells under the pressure of the expanding duct. (Hematoxylin and eosin; × 135.)

epithelial lining of the ducts from stripping of the single layer of cells from the wall due to a technical artefact in the preparation of tissues. The most reliable evidence that denudation of the wall was due to pathologic effects was the presence of a marked thinning or flattening of the cells in adjacent areas. Separation of an otherwise normal columnar epithelium was viewed as an artefact.

Well advanced flattening of epithelium from increased intraductal pressure is shown in figure 3*b*. The outlines of the cells are indistinct, and many of the nuclei are atrophic or pyknotic. This change apparently occurs much earlier in the duct of Wirsung than in the smaller ducts or tributaries, and the explanation of this is not clear. Table 2 discloses that flattening of the epithelium occurred in a variable degree in every specimen, though not in every section of tissue. The duct of Wirsung showed denuded areas in all but 4 specimens. The mechanism of denudation is not clear. The cells may slough off the wall of the duct from diminishing intraductal pressure in later stages of the obstructive process, or the separation may result from degeneration and thinning of the wall itself.

Thinning of Walls of Ducts.—This occurred to a marked degree, especially in the chief duct, in all but 1 specimen. Here again the change was much less noticeable or often absent in the smaller tributaries. In 1 specimen (fig. 4*a*) the wall was practically destroyed, so that only a ghost channel remained in the fibrosed pancreatic skeleton. It is probable that the elastic tissue disappears as well as the collagen, although sections were not stained for elastic tissue. This is considered the final stage in degeneration of the duct. Probably degeneration would progress to this stage in every case if the patient survived long enough. Papillary forms of epithelium projecting into the lumen were not seen in any stage of the process.

Lesions of the Duct of Wirsung.—The separation of the normal epithelial lining of the duct of Wirsung which produces a serrated effect was probably due to shrinking of the wall of the duct during fixation and should not be considered a pathologic alteration. Flattening and desquamation of the epithelial lining and thinning of the wall of the duct were the chief pathologic changes noted in the duct of Wirsung, and every specimen revealed one or more of these changes. As a rule, these changes were much more advanced in the duct of Wirsung than in its tributaries or smaller excretory ducts. Low grade periductal inflammation was not infrequently noted.

Lesions of the Smaller Ducts.—In the sections of tissue of 7 specimens (28 per cent) the smaller ducts appeared normal in all respects. In 9 specimens (36 per cent) the changes were minimal and consisted of flattening of the cells of the epithelial lining. In the remaining 9 specimens the changes were more pronounced, consisting of flattening

and occasional desquamation of epithelium with moderate thinning of the walls of ducts. The most impressive alteration encountered in the smaller ducts of the whole series is demonstrated in figure 3*a*.

Acinar Destruction.—As might be expected logically, the degree of acinous atrophy and destruction was found to be roughly proportional to the degree of interlobular and interacinar fibrosis. The earliest change in the process of acinar destruction was probably dilatation of acini. This change, however, was either slight or absent in almost half of the cases (48 per cent). The possibility that dilatation had occurred earlier in these cases and was followed closely by atrophy and disappearance of cells has been considered likely but could not be verified in this study. The acini seemed to be rapidly replaced by fibrous tissue soon after their dilatation and the atrophy and disappearance of the acinar cells. Severe dilatation of the acini (grade 3; fig. 4 *b*) was observed in 19 per cent of the cases and moderate dilatation in 33 per cent. It is undoubtedly correct to state that the destruction of acini occurred primarily as a result of obstruction of the ducts and not as a result of fibrosis. The external pressure of dilated ducts often compressed adjacent acini into thin cords or strands of atrophic cells, which finally disappeared (fig. 3*b*). Evidence of active inflammation was not seen often in this process of slow atrophy and fibrous replacement. In figure 4*b* acinous destruction, grade 3, and abundant fibrosis are evident; yet there is no evidence of inflammation such as would be reflected by the presence of polymorphonuclear leukocytes or lymphocytes. Fat necrosis (fig. 5*a*) and the presence of lymphocytes in the surrounding tissue represented a residual lesion which was probably the end result of rupture of acini much earlier in the process.

Interlobular and Interacinar (Intralobular) Fibrosis.—Fibrosis was undoubtedly the most pronounced and conspicuous change. In 11 specimens (44 per cent) the entire pancreas exclusive of the carcinomatous portion was transformed into a mass of fibrous tissue, deteriorating ducts and persistent islands of Langerhans. Pathologic phenomena involving the duct of Wirsung and smaller ducts tended to parallel the degree of total replacement with few exceptions. The question arises how much of the fibrosis was due to the desmoplastic property of pancreatic carcinoma as opposed to the degeneration or previous inflammation incident to obstruction of the ducts. This will be discussed presently. In 3 specimens the interlobular fibrosis was only of grade 1 and in these little or no intralobular (interacinar) fibrosis was apparent. Interlobular or intralobular fibrosis, grade 3 or 4, was present in 18 specimens (72 per cent). A comparison of the degrees of fibrosis and gross fatty replacement of the organ shows no parallelism between the two processes. Various stages of intralobular (interacinar) fibrosis were observed, and the degree was usually commensurate with the

extent of interlobular fibrosis. An excellent example of intralobular fibrosis, grade 3, is seen in figure 4 *b*. The destroyed acinar cells were being gradually replaced by fibrous tissue as the latter followed in the wake of the destruction of acini.

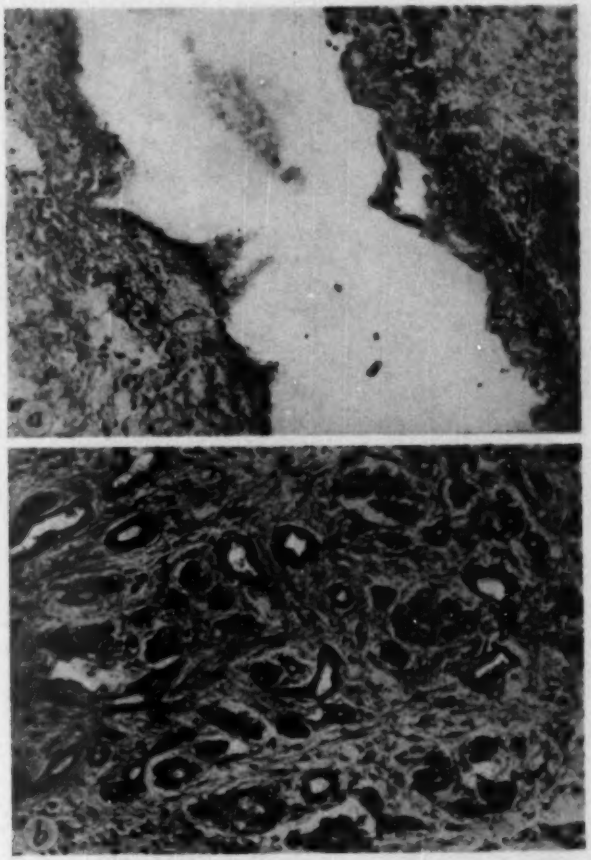

Fig. 4.—(*a*) Part of the duct of Wirsung in the most advanced stage of destruction. The epithelium has long been sloughed off, and the collagenous and the elastic wall have atrophied almost completely. What remains is virtually a ghost channel in the fibrosed pancreatic skeleton. (Hematoxylin and eosin; × 155.) (*b*) Intralobular (interacinar) fibrosis, dilated acini and atrophied and disintegrated individual cells of acini can be seen. Islets can be seen, which also are somewhat atrophied. (Hematoxylin and eosin; × 175.)

Pancreatitis and Fat Necrosis.—In 16 specimens (64 per cent) variable degrees of pancreatitis and fat necrosis were evident. In only 3 specimens (12 per cent) was there definite evidence of acute focal pancreatitis, characterized chiefly by collections of polymorphonuclear

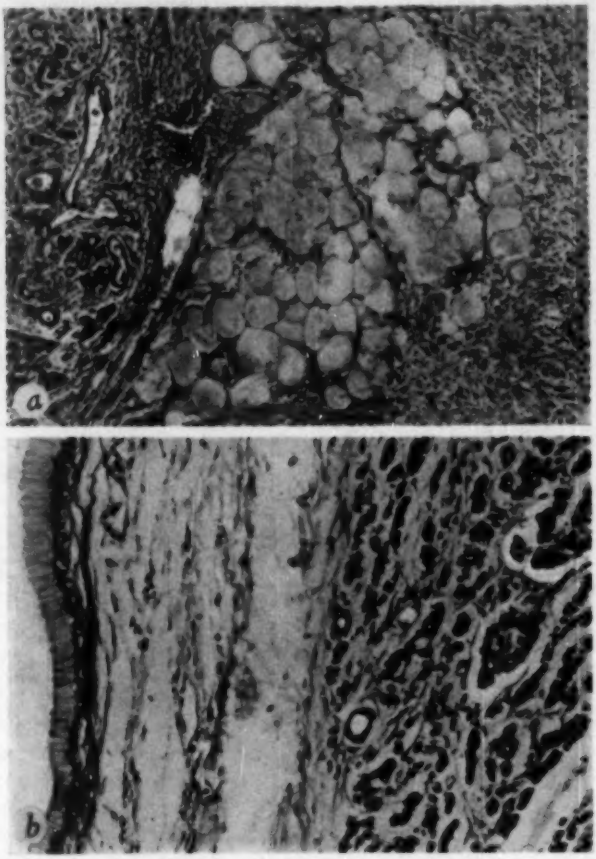

Fig. 5.—(*a*) An area of fat necrosis with lymphocytic infiltration, denoting chronic pancreatitis. Evidence of marked interlobular and interacinar fibrosis, dilated acini and atrophy of individual cells is present. (Hematoxylin and eosin; × 75.) (*b*) Wall and lining of a retention cyst. The single layer of columnar epithelium has not become flattened, but some of the nuclei appear pyknotic. Note the destruction of cells of acini by compression effects of the cyst. Interacinar fibrosis is mild. (Hematoxylin and eosin; × 170.)

leukocytes (table 2). It is entirely possible that the incidence of fat necrosis and pancreatitis is considerably greater, since healing is known to occur, leaving no evidence in its wake but fibrosis. Thus in at least 6 specimens which manifested fibrosis, grade 3 or 4, there may well have been previous pancreatitis and fat necrosis. A severe degree (grade 3) of chronic pancreatitis, characterized chiefly by areas of infiltration of lymphocytic and plasma cells, was observed in only 2 cases.

Pseudocysts and Retention Cysts.—In 7 specimens (28 per cent) gross cystic changes of either the pseudocystic or the retention type were exhibited, and microscopically cysts of one or the other type or both could be identified in all of these. Retention cysts (fig. 5*b*) were

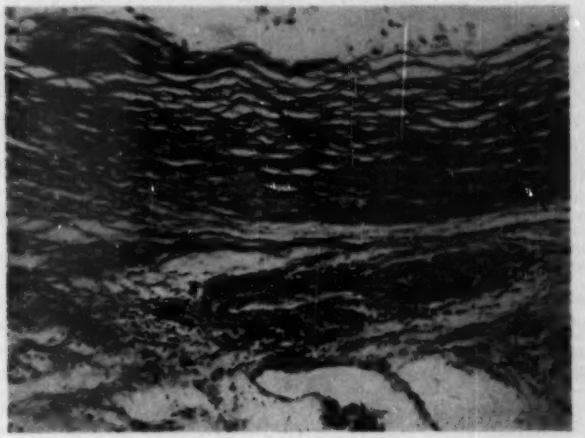

Fig. 6.—Lining of a pseudocyst which measured 1.0 cm. in diameter. Note the thick, dense fibrous wall. The absence of epithelial lining and of any outlet communicating with the ductal system characterized this as a pseudocyst. Note hemosiderin and lymphocytes. (Hematoxylin and eosin; × 85.)

found microscopically in 5 specimens and pseudocysts (fig. 6) in only 4. It was impossible to be certain that some of the pseudocysts were not actually retention cysts which had lost their epithelial lining as a result of pressure, because it was most difficult to be sure in all instances that no ductal communication existed. Both types of cysts produced effects of compression of surrounding acini similar to those encountered in the vicinity of dilated ducts.

On the basis of this investigation, cystic changes are probably more frequently a sequel to obstruction of the duct due to carcinoma of the head of the pancreas than is generally supposed (tables 1 and 2).

In case 18, in which the specimen was a mass of cysts, microscopic examination of several sections of tissue failed to disclose any epithelial lining in the cysts. The most conspicuous feature was a rather dense and thick fibrous wall. This observation, together with the fact that there was no evidence of any intercommunication of the cysts and the ductal system on gross investigation, characterized the change as pseudocystic. It is reasonable to assume that the cystic change could have resulted from multiple areas of focal pancreatitis and that fat necrosis caused by rupture of acini in the presence of increasing intraductal pressure was probably the immediate cause. This conclusion is strengthened by the fact that the patient suffered rather severe constant epigastric pain for about twelve weeks before death. Why such extensive cystic degeneration should not occur more frequently in cases of complete

TABLE 2.—*Analysis of Changes in Head, Body and Tail of Pancreas in 25 Cases*

	Number of Specimens Showing Given Grade of Severity * of Change in Head and Body					Number of Specimens Showing Given Grade of Severity * of Change in Tail				
Pathologic Condition	0	1	2	3	4	0	1	2	3	4
Desquamation of epithelium	6	2	6	4	7	5	3	7	6	2
Flattening of epithelium	3	7	7	3	5	1	6	11	5	2
Thinning of wall	1	1	10	12	1	3	2	6	15	0
Interlobular fibrosis	2	3	2	6	10	1	3	5	6	10
Intralobular fibrosis	4	2	5	2	12	2	3	6	3	11
Acinar destruction	2	3	3	6	11	2	1	5	7	10
Amount of fat necrosis	13	6	6	0	0	11	9	4	1	0
Acute pancreatitis	22	3	0	0	0	25	0	0	0	0
Chronic pancreatitis	12	6	6	1	0	9	5	10	1	0
Pseudocysts (microscopic)	22	2	1	0	0	23	1	0	1	0
Retention cysts	23	1	0	1	0	20	2	3	0	0

* Severity is graded on the basis of 1 to 4, 1 being the least change and 4 the greatest. Zero means that the specimen showed no change or was normal in that respect.

obstruction of the pancreatic duct aroused our curiosity. In case 18 the cysts of the specimen were filled with rather thick grayish gelatinous material, which was washed out in the process of fixation and therefore could not be studied microscopically.

COMMENT

The obvious and striking gross changes occurring in the pancreas, such as fatty replacement, increase of density, atrophy, formation of cysts and dilatation of the duct of Wirsung, hardly merit extensive discussion. It should be reiterated that the extent to which the organ was replaced by fat did not necessarily parallel the degree of atrophy and fibrosis, although there appeared to be a direct relationship between the extent of fatty replacement and the degree of dilatation of the duct.

Atrophy results primarily from loss of acinar tissue. The formation of cysts is not as easily explained, since it is not a constant occur-

rence. Why retention cysts occur in one specimen and not in another when both present complete obstruction of the pancreatic duct of probably equal duration is a mystery. The occurrence of pseudocysts can be explained easily on the basis of focal areas of acute pancreatitis and fat necrosis, but the problem here is to explain why pancreatitis and fat necrosis were not observed in every case of complete obstruction. Perhaps in some cases the neoplastic obstruction closes off the duct of Wirsung so gradually that the pressure head in the ductal system is not great enough to rupture the acini early in the process. In that event the dilatation of acini and the atrophy of cells could continue beyond the stage of enzymatic secretion. If the acini ruptured at this later stage, the effects should be innocuous. Such a theory would be consistent with the finding by many investigators that one of the earliest changes to occur in experimental ligation is the disappearance of granules of zymogen, the source of pancreatic enzymes. Another possibility is that in some cases a slowing of the stream in the ducts may cause chemical alterations which could result in inspissation or plugging of the smaller ducts and consequent rupture of actively secreting acini. The result, of course, would be focal areas of acute pancreatitis and perhaps fat necrosis. It is not unreasonable to postulate that variable degrees of acute or chronic pancreatitis may have been present in nearly all cases in this series at some time or other in the obstructive process. This theory is in accord with that of Rienhoff and Pickrell.[8]

It may be that all these changes actually occur, depending on the conditions described. Cystic changes are probably rare after experimental ligation of the duct of Wirsung; at least in the papers reviewed, Kodama [2] was the only one who mentioned "cystic degeneration" in later stages after ligation of the ducts of rabbits.

Although specific measurements of the degrees of dilatation of the pancreatic duct in experimental ligation have apparently not been taken, it is doubtful that the dilatation is as marked, relatively speaking, as that seen in carcinomatous obstruction. It is entirely possible that in the latter situation most of the dilatation occurs before the duct is completely obstructed. Certainly it must occur while the acini are still actively secreting. There is an interesting analogy to enhance the logic of this statement. It has long been known that tying off a ureter (sudden obstruction) causes minimal hydronephrosis, while gradual constriction of a ureter effects extreme hydronephrosis.

As previously mentioned, two types of dilatation of the duct were observed, namely, cylindric and saccular, the latter being much commoner.

Perhaps the unequal thickness of the collagenous connective tissue of which the pancreatic ducts are composed accounts for the greater

8. Rienhoff, W. F., Jr., and Pickrell, K. L.: Arch. Surg. **51**:205, 1945.

tendency toward saccular dilatation. It seems that the wall of a duct would naturally yield most readily in the thinnest areas. However, the supportive resistance offered by the surrounding parenchyma may also play a significant, if not a more important, role. Hence, if degeneration, necrosis or atrophy occurs in the tissues immediately surrounding the duct, little or no counterpressure is offered and the wall of the duct may expand enormously, whereas in areas where abundant fibrosis surrounds the duct, the wall may be much less yielding.

The theory of unequal thickness of the wall of the duct is least tenable in the explanation of the cylindric type of dilatation. In cases of the cylindric variety a striking feature was the firmer, almost cartilaginous consistency of the organ throughout the area of cylindric dilatation. Perhaps this homogeneous consistency tended to prevent saccular bulging of the duct. The effect of the comparison is heightened in cases of the saccular variety by the presence of cleftlike bands of fibrous tissue between the saccules, which again lends credence to the view that the wall itself is much more resistant in certain areas than in others.

It may be said, then, that the type of dilatation may be influenced by the thickness of the wall and by the resistance offered by the surrounding tissue. It is obvious that a thin wall or areas of degeneration, necrosis and atrophy of the surrounding parenchyma would favor dilatation more than would a thick wall or one supported by thick, dense fibrous tissue. Thus, in case of the cylindric variety the surrounding organ is uniformly firm throughout the area of dilatation whereas in cases of the saccular variety the fibrosis is much less uniform, tending to occur in the clefts between the saccules as bands of fibrous tissue.

Certain facts peculiar to the accessory duct of Santorini may prove of importance when the chief duct is obstructed at a point distal to the bifurcation of the two ducts. Simkins [9] studied variations of the duct of Santorini in 25 cases and showed that while the minor papilla was probably always present, in only 10 per cent of the cases was the minor papilla patent enough to function as a safety valve should the duct of Wirsung be obstructed or under increased pressure.

In 2 of Simkins' cases the duct of Santorini retained its early embryonic arrangement and was actually the chief duct of the gland. Opie [10] reported that in 10 per cent of cases the duct of Santorini was as large as, or larger than, the duct of Wirsung. Neither of these last two statements is borne out in the 25 cases which we studied. It is well to remember that, unlike the duct of Wirsung, the duct of Santorini diminishes in caliber as it approaches the intestine, since it normally

9. Simkins, S.: Am. J. M. Sc. **182**:626, 1931.

10. Opie, E. L.: Disease of the Pancreas: Its Cause and Nature, ed. 2, Philadelphia, J. B. Lippincott Company, 1910.

atrophies completely in its terminal portion in a large percentage of specimens. These facts, together with the likelihood that the accessory duct and the duct of Wirsung are completely obstructed or obliterated, as is true in nearly all instances of advanced carcinoma of the head of the pancreas, make it evident why the duct of Santorini rarely acts as a shunt or a safety valve in cases of neoplastic invasion of the head. Its clinical importance is thus almost negligible in such processes except when anomalies prevail.

In the 10 normal specimens the average circumference of the chief duct of the pancreas in the region of the head and neck was 0.64 cm., compared with an average circumference of 2.25 cm. for the pathologic duct measured in approximately the same region. These figures for the normal duct compare well with those of Baldwin,[11] who found a mean "diameter" (flattened duct) of 3 mm. Since the measurement of the flattened duct is actually half the outer circumference, the mean circumference for the 66 cases which he studied would be 6 mm. or 0.6 cm. In our opinion a circumferential measurement is more accurate than a diametric measurement of a "flattened duct," but it must be remembered that Baldwin utilized 66 cases, compared with 10 cases in our series. In our series each specimen was dissected only a few hours after death occurred. On the basis of normal caliber the duct of Wirsung is capable of dilating to more than three and a half times its normal circumference. In the tail the elasticity is slightly less impressive even when the smaller caliber of the duct in this region is considered. In 25 specimens the average dilatation was slightly less than three times the normal circumference. At least part of this discrepancy could have been caused by experimental error. Advanced age does not seem to lessen the tendency toward great dilatation. The specimens from 3 patients who were more than 68 years of age exhibited maximal dilatations of the duct of Wirsung of 7 cm. or more. Evidence could not be found to indicate that the duct of Wirsung or its major tributaries had ruptured suddenly at any stage of the obstruction, as it has been seen to do in experimental ligation.[2] Rupture is probably restricted to dilated acini.

Histologically, fibrosis was the most pronounced of all changes (table 2). Except for persisting islands of Langerhans, fibrosis, grade 4, of both the interlobular and intralobular (interacinar) types occurred in 12 cases in either the head and body or the tail, or in all 3 areas. Barron [1] described overwhelming fibrosis involving the entire organ in cases of obstruction of the duct due to pancreatic lithiasis. In the end stages of experimental ligation of the duct of Wirsung there was abundant interlobular and interacinar fibrosis, and yet carcinoma was not present. The changes shown in the photomicrographs in Barron's

11. Baldwin, W. M.: Anat. Rec. **5**:197, 1911.

paper bear a striking resemblance so far as severity is concerned to those which we have illustrated. These similarities have caused us to conclude that the changes herein described resulted from obstruction.

Microscopic study of the ductal system did not yield results entirely in accord with those mentioned by Grauer [5] and Barron [1] in their incidental descriptions. None of the 25 specimens showed what Grauer termed "papillary hyperplasia" of the ducts. Barron maintained that attempts at regeneration occur rather early in the ducts. The results of our investigation and of Grauer's study, however, strongly suggest that the increased number of ducts in certain sections of tissue is more apparent than real, the appearance of an increase being due to destruction of acini and to atrophy and condensation of tissue with persistence of practically all the original ducts in the remaining pancreas. Squamatization of the epithelial lining of obstructed pancreatic ducts has been described as conspicuous by Pasternack,[12] who mentioned that desquamation of such epithelium may serve as a nidus for calcification in the ducts. In none of the 25 specimens in our study were areas of squamous metaplasia or calcification observed in the ductal system. While it is not denied that both squamatization and calcification may be seen in cases of obstruction of the pancreatic duct, these findings are probably exceptional.

Regeneration of acini observed by Bensley [13] and others in guinea pigs in which the pancreatic duct had been ligated was not observed in any of our 25 specimens, and it is likewise doubtful that actual regeneration of islets occurred, although the latter subject demands a separate investigation for final proof or denial.

The observation by Milne and Peters [14] that there is a tendency toward reestablishment of excretory channels in guinea pigs, dogs, cats and rabbits in which the pancreatic duct has been ligated is not paralleled in our study of obstruction of the duct from carcinoma in the head of the pancreas.

It is of considerable interest that in only a few cases (19 per cent) was there severe dilatation of the acini. Even in these cases the degree of dilatation was not as great as that commonly observed in cases of so-called cystic fibrosis of the pancreas, and inspissated and laminated secretion was not observed (fig. 4*b*). This is not, however, considered as a serious objection to the theory that ductal obstruction is a cause of cystic fibrosis of the pancreas, since the latter condition is observed in pancreases of children only and our study was concerned with adult patients. Presumably the response to ductal obstruction in the growing gland of a child may be quite different from that in the gland of an adult.

12. Pasternack, J. G.: Am. Int. Med. **19**:757, 1943.

13. Bensley, R. R.: Am. J. Anat. **12**:297, 1911.

14. Milne, L. S., and Peters, H. L.: J. M. Research **26**:405, 1912.

CORRELATION OF CLINICAL AND PATHOLOGIC OBSERVATIONS

The correlation of clinical records and total alterations of the pancreas in our series of 25 cases suggests that approximately three months may be the average time required to produce these effects. Thompson and Abe [15] postulated a similar interval of time for a case which they observed. The time estimated as necessary to destroy the portion of the pancreas which produces exocrine secretions in animals in which the pancreatic duct has been ligated has been stated variously to be from two to ten weeks.[16]

It is of interest to compare the pathologic observations in the 25 specimens with the clinical and laboratory findings which may be related to pancreatic dysfunction. In 8 cases the concentrations of serum amylase ranged from 50 to 320 units. The concentrations of lipase were determined for 5 patients, and in each instance the results were likewise normal. Thus in 8 patients the concentrations of the serum amylase and lipase were within the normal range, although the pancreases of 5 of the 8 patients showed definite areas of fat necrosis and evidence of pancreatitis. That the concentrations of these enzymes in the serum were normal was not surprising in view of the extensive damage to and destruction of the acinar cells.

Determinations of blood sugar had been carried out for 7 patients who were suspected of having diabetes. In 3 cases (12 per cent) diabetes was definitely diagnosed, and the duration of symptoms suggested that it did not antedate the onset of pancreatic disease. A disturbance of blood sugar levels of 4 other patients was reflected in mild glycosuria or hyperglycemia or both, but a definite diagnosis of diabetes was not made. It is of interest to compare these observations with those of Grauer,[8] who found that 8 of his 34 patients (23 per cent) had increased concentrations of blood sugar. It is possible that in cases of carcinoma of the head of the pancreas with obstruction of the pancreatic ducts diabetes develops more frequently than is generally supposed. It should be termed properly "pancreatic diabetes," not "diabetes mellitus." In all 3 cases of diabetes the pancreas showed severe grades of interlobular and intralobular fibrosis, while in the remaining 4 the pancreatic changes were milder.

The clinical histories of all 25 patients were reviewed from the standpoint of gastrointestinal disturbances which might be related to pancreatic exocrine dysfunction. It was found that only 3 patients (12 per cent) had exhibited definite diarrhea, and the stools were not described. As to the remaining patients, the normal function of the bowels, or constipation, or discoloration ("clay color") of stools was noted. Mention was not made of so-called steatorrhea in any case.

15. Thompson, R. T., and Abe, G. Y.: Ohio State M. J. **41**:46, 1945.
16. Arnozan and Vaillard: Arch. de physiol. norm. et path. **3**:287, 1884.

The part played by biliary obstruction in the gastrointestinal disturbances of these patients is somewhat minimized by the fact that 14 patients (56 per cent) had undergone palliative anastomosis, such as cholecystogastrostomy, choledochoduodenostomy or choledochostomy.

SUMMARY AND CONCLUSIONS

The pathologic changes incident to neoplastic obstruction of the pancreatic ducts were studied in an attempt to establish a clearer concept of the gross and histologic alterations that result from an insidious type of obstruction which in our 25 specimens proved to be complete.

In neoplastic obstruction of the pancreatic ducts the earliest changes are distention of the ducts and flattening of the epithelial lining. Soon thereafter desquamation of the epithelium, thinning of the walls of the ducts and variable degrees of dilatation occur, but it is doubtful that rupture of large ducts occurs during the period in which the acini are actively secreting. Dilatation and occasional rupture of acini probably occur during the active stage of secretion, and it is considered that most of the focal areas of pancreatitis and fat necrosis are initiated in a similar manner. Later in the process nearly all acinar tissue is replaced by fibrous tissue, and this replacement becomes the most conspicuous change in the entire organ.

Dilatation of the duct of Wirsung appears to be more marked in cases of obstruction caused by cancerous growth than in cases of experimental ligation. Neither squamatization nor calcification occurred in the obstructed ducts. Regeneration of ducts or acini could not be demonstrated in any of the specimens. A direct relationship apparently exists between the extent of acinar destruction and the degree of dilatation of the ducts. In general a direct relationship appears to exist between the extent of fatty replacement in the pancreas and the degree of ductal dilatation. In our series of 25 cases the duct of Wirsung was found dilated to an average of three and a half times the size of the normal duct.

It seems to us that cases of neoplasm of the pancreas such as those we have studied will afford a good opportunity to the clinician and the physiologist to study certain changes in the digestive processes due to deprivation of pancreatic exocrine secretions. This is especially true in the instance of patients devoid of metastasis who have undergone palliative cholecystogastrostomy or choledochoduodenostomy. In such patients the flow of bile has been restored and thereby confusion in analysis of the disturbances would be prevented.

GENERALIZED ASPERGILLOSIS

Report of a Case

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THE SPECIES of the genus Aspergillus are notorius saprophytes. However, on occasion, various members of the group may be encountered as pathogens.

The disease aspergillosis is most frequently limited to the pulmonary system and is usually caused by A. fumigatus. As early as 1897, Rénon [1] recognized pulmonary aspergillosis as an occupational disease in wigmakers and pigeon feeders. The wigmakers used corn meal for freeing the hair from oil, and the pigeon feeders chewed grain, which they then forced from their own mouths into the beaks of squabs in order to fatten them rapidly. In 1945 Coe [2] reported the first case of pulmonary aspergillosis to be tried before an industrial commission and to be declared a case of occupational disease. The patient had worked in the stockyards for twenty years and had been exposed to heavy concentrations of dust, which included dusts of hay, grain, straw, corn and animal dander.

The pulmonary picture of aspergillosis may simulate that of acute bronchopneumonia,[3] tracheobronchitis [4] or pulmonary tuberculosis.[5] In many instances, pulmonary aspergillosis is apparently a secondary infection, being superimposed on tuberculosis, bronchiectasis and carcinoma [6] and occurring even after a heavy chest cold.[4] There are no characteristic roentgenologic features.

Aspergillosis of other organs has been reported infrequently, and in most instances it has been associated with pulmonary aspergillosis.

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1. Rénon, L.: Etude sur l'aspergillose chez les animaux et chez l'homme, Paris, Masson & Cie, 1897.
2. Coe, G. C.: Ann. Int. Med. **23**:423, 1945.
3. Cooper, N. S.: Arch. Path. **42**:644, 1946.
4. Coon, E. H.; Smith, H. B., and Walsh, J. C.: M. Times **74**:225, 1946.
5. Van Ordstrand, H. S.: Cleveland Clin. Quart. **7**:66, 1940.
6. Kampmeier, R. H., and Black, H. A.: Am. Rev. Tuberc. **30**:315, 1934.

A cerebral abscess caused by an Aspergillus has been reported, as has a fatal case of aspergillus meningitis (Just[7]; Linck[8]). Lesions of the spleen, kidneys, duodenum, lymph nodes[9] and bones[10] have also been reported, and the Aspergilli have also been incriminated as the cause of blepharitis and dacryocystitis[12] and in some cases onychomycosis.[11]

We have been able to find only 1 case of generalized aspergillosis described previously. This case was reported by one of us,[13] and the patient had involvement of the brain, dura, heart, lungs, mediastinum, lymph nodes, spleen, liver, kidney and bones. Another case of generalized aspergillosis has recently been encountered in this hospital and is reported here.

REPORT OF CASE

R. W., a 22 year old white male molder, noticed the onset of cough, fever, chills and aching pains in the joints early in October 1948. He was given penicillin and other medications by a physician without effect. On October 24 he consulted another physician, whose description of the case follows: The patient appeared to be acutely ill, had a temperature of 104 F. and was expectorating a thick, purulent sputum. There were coarse rales throughout both lung fields. He complained of a sore mouth, and the oral mucous membranes were reddened and covered with a patchy exudate. He also had an erythema multiforme type of eruption, which was presumably due to the penicillin administered previously. A roentgenogram of the chest revealed pneumonitis in the middle and lower lobes of the right lung. The hemoglobin content was 76 per cent. The red blood cell count was 3,460,000, and the white cell count 7,450, with polymorphonuclear leukocytes 72 per cent, lymphocytes 27 per cent and monocytes 1 per cent. He was given a short course of sulfadiazine as an outpatient, and his condition improved for a short time, the fever diminishing and the aches subsiding. However, he continued to raise considerable quantities of thick sputum, and the rales persisted. About the middle of December 1948 he had swelling and pain in the left wrist and both shoulders. In the latter part of the same month he received 20 Gm. of aureomycin over a ten day period. His temperature remained between 99 and 101 F. Blood agglutination tests for undulant fever, typhoid, tularemia and psittacosis were negative. The heterophil agglutination test was negative. The Weil-Felix reaction was negative. Four pooled sputum specimens did not show acid-fast bacilli. A tuberculin test with 1.0 mg. of old tuberculin was negative. The histoplasmin skin test was also negative. About the end of December 1948 the patient's course suddenly became worse. His temperature rose to 104 F., more sputum was produced, anorexia developed and severe generalized aching made it uncomfortable for him to move. There were also periods during which he was irrational. He was hospitalized on Jan. 4, 1949. At that time the hemoglobin content was 74 per cent, the red blood cell count 3,700,000 and the white blood cell count 8,000, with a normal differential count. Three transfusions of 500 cc. of whole blood elevated the hemoglobin content to 90 per cent and the red blood cell count to 4,700,000. One-half gram

7. Just, E.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **42**:540, 1931.
8. Linck, K.: Virchows Arch. f. path. Anat. **304**:408, 1931.
9. Wahl, E. F., and Erickson, M. J.: J. M. A. Georgia **17**:341, 1928.
10. Shaw, F. W., and Worthen, H. J.: South M. J. **29**:1070, 1936.
11. Bereston, E. S., and Waring, W. S.: Arch. Dermat. & Syph. **54**:552, 1946.
12. Rosenvold, L. K.: Am. J. Ophth. **25**:588, 1942.
13. Cawley, E. P.: Arch. Int. Med. **80**:423, 1947.

of streptomycin was administered every six hours. The temperature curve continued to spike to 104 F., and his condition became steadily worse.

The patient was transferred to the University of Michigan Hospital on January 16. The physical findings at that time were as follows: The temperature was 103.6 F.; the pulse rate, 180; the respiratory rate, 28, and the blood pressure, 70 systolic and 50 diastolic. He was irrational and irritable. There was a large, firm nodule in the left frontal area, the overlying skin being of normal color. The gums bled easily, and there were small ulcers of the tongue. There were several palpable discrete, small, firm, nontender cervical and axillary nodes on the right.

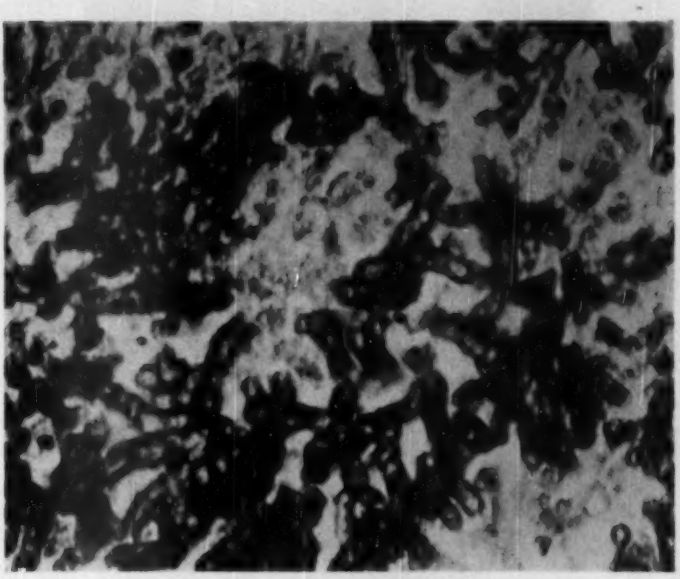

Fig. 1.—Photomicrograph of a pulmonary lesion showing numerous hyphae and spores (high power).

There were moist rales throughout the entire chest, with occasional wheezes and rhonchi. The right lower part of the chest was dull to percussion. The liver was palpable 2 fingerbreadths below the right costal margin. Neurologic examination revealed definite nuchal rigidity. The reflexes were hypoactive to absent throughout, and Babinski's reflex was present on the right. There was blurring of the nasal margins of both optic disks.

Examination of the urine revealed albuminuria (2 plus) and 2 to 4 red blood cells per high power field. The hemoglobin content was 9.5 Gm.; the red blood cell count, 3,800,000; the white cell count, 27,450, with polymorphonuclear leukocytes 93 per cent, lymphocytes 5 per cent and monocytes 2 per cent. Lumbar puncture revealed a clear spinal fluid with a pressure of 140 mm. of water. There

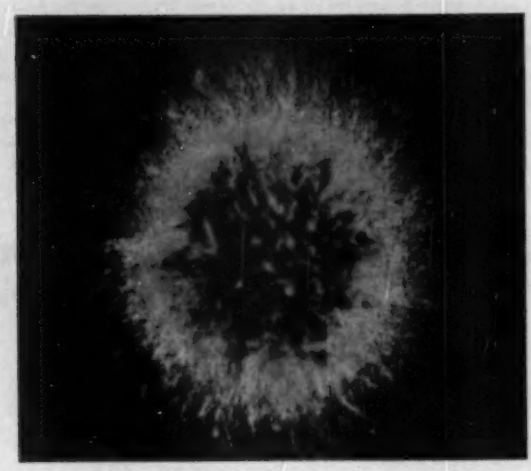

Fig. 2.—Culture of Aspergillus fumigatus obtained from pulmonary tissue.

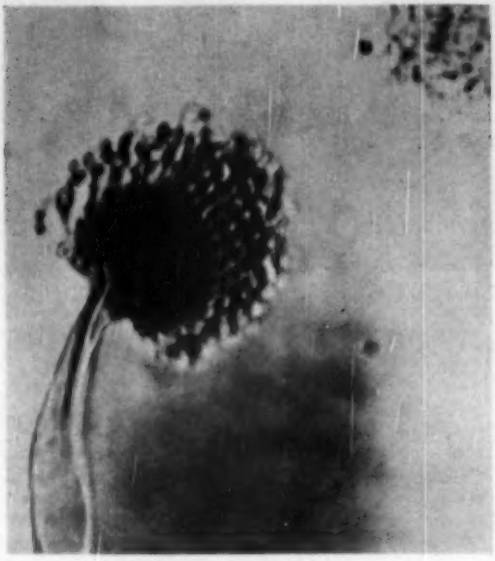

Fig. 3.—Culture mount of Aspergillus fumigatus showing fruiting body with attached spores.

were 6 cells per cubic millimeter of spinal fluid. No organisms were seen. The spinal fluid was cultured for pyogenic organisms but revealed none. Blood cultures were negative. A roentgenogram of the chest revealed pneumonitis in the middle and lower lobes of the right lung with atelectasis of the lower lobe.

The patient had become comatose, and an intracranial lesion was suspected but not demonstrated by ventriculography or ventriculoscopy. Respirations ceased on January 18, forty-eight hours after his admission.

A complete necropsy was made. Microscopic examination of the brain revealed fungi with spores and hyphae in tissue. There was also subarachnoid and intraventricular hemorrhage. There were focal subacute granulomas in the myocardium and subendocardium, some of which contained filaments and spores. The lungs revealed confluent lobular pneumonia and numerous granulomas containing sporulating hyphae (fig. 1). There were numerous fungi in the large bronchi and granulomatous ulcers of the bronchial, laryngeal and tracheal mucosae. Mycotic granulomas were also demonstrated in the thyroid gland, duodenum and kidneys. Cultures of pulmonary tissue revealed a pure growth of fumigatus (figs. 2 and 3).

ANIMAL INOCULATION STUDIES

Because of the ubiquity of the Aspergilli, we were interested in knowing whether A. fumigatus isolated from human tissues would react differently in animals from cultures of the same organism encountered as a contaminant.

Saline suspensions of cultures obtained in 4 cases (the present case, another reported by one of us,[13] a case of pulmonary aspergillosis involving a patient whom we have been following in the outpatient clinic, and a case of aspergillus contamination of Sabouraud's medium) were prepared, and 1 cc. amounts of the suspensions were injected intraperitoneally into guinea pigs respectively. The animals experienced no noticeable reaction. Necropsy was performed ten days after injection, and all tissues were normal. Cultures of various organs were negative.

Cooper [2] injected into the tracheas of rabbits suspensions of spores of a culture of material in a fatal case of bronchopneumonia due to A. fumigatus. In twenty-four to forty-eight hours he found acute bronchopneumonia with many fungous elements present. In from six to twenty-six days the acute character of the lesions was lost and a granulomatous reaction occurred. No organisms could be found, and cultures were negative. In seventy-three days all signs of lesions had disappeared, and cultures were negative. All these rabbits had to be killed for necropsy. He also injected the fungus into 1 rabbit intravenously, and this animal died within twenty-four hours. Miliary abscesses were demonstrated in heart, lungs and liver. A pure culture of A. fumigatus was obtained from the blood but no hyphae could be found histologically.

Donaldson, Koerth and McCorkle [14] also injected into a rabbit intravenously a suspension of a culture obtained in a case of pulmonary aspergillosis. The rabbit died in three days, and necropsy revealed large hemorrhagic areas throughout both lungs, the liver and the spleen and petechial hemorrhages in the cortex of each kidney. The fungus was recovered in pure culture from the spleen.

Lapham [15] presented 10 cases of primary pulmonary aspergillosis in which the organisms showed a high and constant virulence for rabbits when injected intravenously.

COMMENT

This, so far as can be determined, is the second reported case of generalized aspergillosis in which almost every major organ of the body was involved.

The results of laboratory studies early in the course of the illness were normal, and the tuberculin test was negative. Lapham [15] has pointed out, however, that in cases of aspergillosis the tuberculin test may produce a positive reaction.

As with Cawley's case, sulfadiazine and penicillin had no apparent effect on the course of the disease. The patient also received courses of streptomycin and aureomycin therapy without effect.

The intraperitoneal inoculation of guinea pigs revealed little. The intravenous route was not used, because it appears from the experience of others that the culture suspension may produce numerous emboli and cause mechanical plugging of vessels.

SUMMARY

An unusual case of generalized aspergillosis caused by Aspergillus fumigatus is reported.

Fungus elements were found in the brain, myocardium, subendocardium, lungs, bronchi, larynx, trachea, thyroid gland, duodenum and kidneys. Cultures of pulmonary tissue showed the organism to be A. fumigatus.

Four guinea pigs were not affected by intraperitoneal injection of three pathogenic strains of A. fumigatus and one strain of the same organism obtained as a cultural contaminant.

The clinical features of the disease and previous animal inoculation studies are briefly reviewed.

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14. Donaldson, J. M., Jr.; Koerth, C. J., and McCorkle, R. G.: J. Lab. & Clin. Med. **27**:740, 1942.

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LESIONS OF GALACTOSE DIABETES

Pathologic Observations

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GALACTOSE diabetes (galactosemia) is a rare metabolic anomaly occurring in infancy and is characterized by the inability of the tissues to metabolize galactose normally. Only 16 cases of the disease have been described and collected to date.[1] That the disease is a familial metabolic defect was indicated by the early report of Göppert,[2] who described 4 siblings with galactosemia.

The essential clinical features of the disease are icterus, hepatomegaly and galactosuria appearing several days after birth. The enlargement of the liver may be associated with signs of portal venous obstruction, which include ascites, splenomegaly and abdominal venous engorgement. Depending on the degree of intolerance to galactose ingested in the infant's milk diet, death may occur early in infancy, or the child may survive, afflicted by severe malnutrition, mental retardation or lamellar cataracts. If recognized early, these pathologic changes may be reversed by eliminating milk, the source of galactose, from the infant's diet. The elevation of the galactose level of the blood with urinary excretion of this monosaccharide when milk or galactose is ingested and the disappearance of galactemia and galactosuria when a galactose-free diet is fed have been recognized for many years.

Mason and Andersen [3] proposed that a defect of the hepatic enzyme system converting galactose to glycogen allows the absorbed galactose

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1. Bell, L. S.; Blair, W. C.; Lindsay, S., and Watson, S. J.: Galactose Diabetes (Galactosemia): Clinico-Pathologic Study of Two Cases, J. Pediat., to be published.

2. Göppert, F.: Klin. Wchnschr. **54**:473, 1917.

3. Mason, H. H., and Andersen, D. H.: Am. J. Dis. Child. **61**:795, 1941.

to pass into the systemic circulation. The total blood sugar then becomes abnormally high, and since galactose cannot be metabolized normally, the circulating dextrose level becomes abnormally low in consequence of accelerated conversion of dextrose to glycogen. Mason and Andersen [3] then believed that the hepatomegaly was due to excessive hepatic storage of glycogen.

More recently Mellinkoff and his co-workers [4] suggested that the hepatic enlargement and diminished function were due to the cellular storage of galactose or its polymer.

In either event the present concept of the hepatic alteration occurring in galactose diabetes is one of abnormal or excessive storage of a carbohydrate in the parenchymal cells. This disease, then, has been considered to be one variant of glycogenosis, or von Gierke's disease.

Although the clinical and laboratory manifestations of the disease have been clearly defined, the exact structural nature of the hepatic abnormality has not been described fully.

Only two brief histologic descriptions of the liver as observed in cases of galactose diabetes have been recorded in the literature. Von Reuss [5] reported the first case in 1908. The infant died at 9 months of age; the clinical diagnosis was hepatic cirrhosis. Autopsy revealed a greatly enlarged liver, richly covered with fine nodules. The lobular markings were indistinct. The hepatic tissue was considerably stained with bile. Microscopic changes included increased interlobular connective tissue, which was infiltrated by lymphocytes. There was parenchymal cellular degeneration. The entire process was considered to be a cirrhosis of the alcoholic type. In a case cited by Goodwin,[6] the liver was malformed, and the hepatic parenchymal cells were described as having an acinous grouping.

The purpose of this report is to describe the pathologic changes, particularly those of the liver, seen in 2 siblings with galactose diabetes. Although galactosemia and galactosuria were not demonstrated in the first sibling, due to its early demise, it has been assumed that both siblings were afflicted with the same disease. In the early stages their clinical courses were identical.[1]

REPORT OF CASES

Case 1.—K. L. was a full term white girl who weighed 3,225 Gm. at birth. The child was normal until the sixth day of life. Death occurred after an illness of two days, which was characterized by vomiting, hematemesis, fever, icterus,

4. Mellinkoff, S.; Roth, B., and MacLaggan, J.: J. Pediat. **27**:338, 1945.

5. von Reuss, A.: Wien. med. Wchnschr. **58**:799, 1908.

6. Goodwin, T. C.: Anomalies of Carbohydrate Metabolism, in Holt, L. E., Jr., and McIntosh, R.: Diseases of Infancy and Childhood, ed. 11, New York, D. Appleton-Century Company, Inc., 1940, p. 1359.

increasing stupor and hepatomegaly. The details of the clinical record are to be published elsewhere.[1]

Autopsy (sixteen hours after death).—Gross Examination: The body measured 51 cm. in length and weighed 3,210 Gm. The skin and the scleras were moderately icteric. The eyes and the ears were normal. Blood was oozing from the nose and the mouth. The umbilical cord was absent, but the umbilicus was covered with dried crusted blood. There was a vesicle measuring 1.5 cm. in diameter on the skin of the left thigh anteriorly. It had a hemorrhagic border.

The abdominal organs lay in their normal positions. The edge of the right lobe of the liver lay 2 cm. below the right costal margin. The serosal cavities had a normal appearance. There were no abnormalities of the thyroid gland. The thymus was smaller than normal but extended down to the base of the heart. It weighed only 2.5 Gm. The heart weighed 17 Gm. There were petechial epicardial hemorrhages along the auriculoventricular sulcus and near the origins of the pulmonary artery and the aorta. The ductus arteriosus was partially occluded by a thrombus, and the foramen ovale was patent. The cardiac valves, the myocardium and the coronary arteries had an entirely normal appearance. There was considerable frothy fluid in the trachea and the major bronchi. The lungs weighed 58 Gm. together. Except for small aerated portions of the middle lobe of the right lung, the lungs were largely atelectatic. The cut surfaces were deeply congested and exuded a moderate amount of sanguinous fluid. There was no consolidation. The liver was enlarged and weighed 137 Gm. There was a sharp lower anterior edge. The external surface was smooth and glistening. Both the external and the cut surfaces had a pale yellow color, with a few poorly defined areas showing pale green pigmentation. There was no grossly evident fibrous accentuation of the hepatic lobular markings. The intrahepatic blood vessels and bile ducts showed no gross abnormalities. The extrahepatic bile ducts and the gallbladder were entirely normal; their lumens were patent. The pancreas was of normal size and consistency. The spleen weighed 8 Gm. and had a normal dark purplish red pulp. The adrenal glands weighed 6 Gm. together. Their cortical and medullary layers were normal; the inner cortical zones were moderately congested. The kidneys were of normal size and weighed 27 Gm. together. The cortical layers appeared unusually pale and were sharply demarcated from the congested medullary portions. There were no abnormalities of the renal pelves, ureters or bladder. The ovaries, uterine tubes, uterus and cervix appeared normal. The bone marrow had normal color and consistency. There was no alteration of the aorta or the inferior vena cava. There was considerable partially digested blood in the stomach. Numerous petechial hemorrhages were present in the gastric and duodenal mucosa. Fewer similar hemorrhages were observed in the remainder of the gastroenteric tract. The scalp contained needle puncture wounds in the region of the anterior fontanel; these were surrounded by areas of hemorrhagic infiltration. The skull was normal. Multiple sections of the brain, after fixation, showed no gross abnormalities. The pituitary gland was of normal size.

Microscopic Examination: All organs and tissues were fixed in dilute solution of formaldehyde U. S. P. and examined microscopically. The majority had normal histologic appearances. Lesions were observed in the lungs, the liver, the kidneys, the thymus and the brain. The pulmonary blood vessels were distended with blood. The majority of the alveoli contained abundant serous fluid and red blood cells. Some contained small amounts of squamous cellular debris and meconium pigment. A few bronchioles and adjacent alveoli contained purulent exudate.

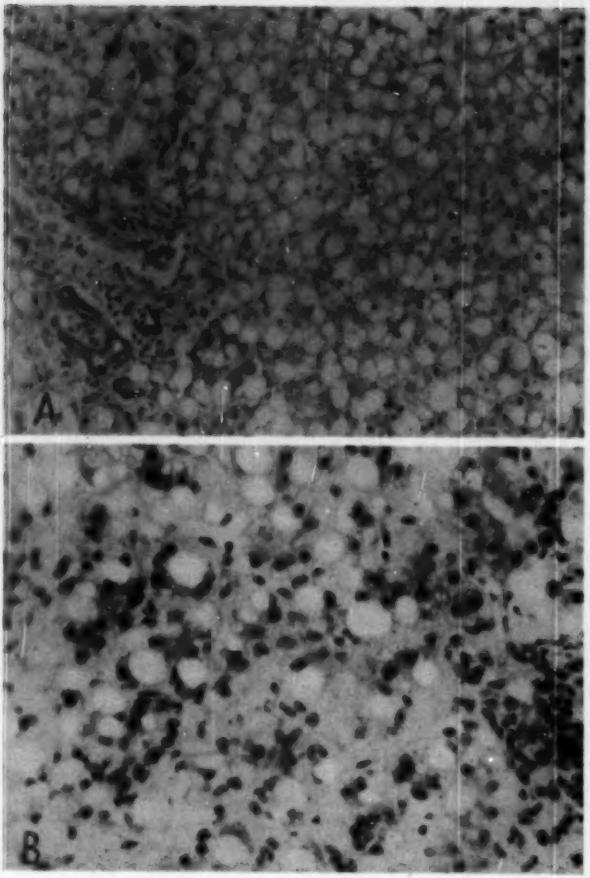

Fig. 1 (case 1).—*A*, liver showing pronounced fatty infiltration. Hematoxylin and eosin; × 160. *B*, liver showing focal accumulations of neutrophilic leukocytes about degenerating hepatic parenchymal cells. Hematoxylin and eosin; × 320.

Almost every hepatic parenchymal cell was distended with a single large clear vacuole, which displaced the nucleus to the periphery of the cell (fig. 1 *A*). Some vacuoles contained yellowish brown ceroid pigment. A narrow rim of hepatic cells with less cellular vacuolation surrounded most portal tracts. Many of the small bile ducts and biliary canaliculi contained bile, particularly at the periphery of the lobules, but these structures were not dilated (fig. 1*B*). The hepatic blood vessels had a normal appearance, and the central veins had a normal position in the hepatic lobules. No collagenous changes were demonstrable with the Mallory connective tissue stain, but in the periportal areas a few young fibroblastic cells had appeared.

There were scattered groups of degenerating or necrotic parenchymal cells surrounded by small accumulations of neutrophilic leukocytes (fig. 1 *B*). These degenerating cells were more numerous adjacent to portal tracts.

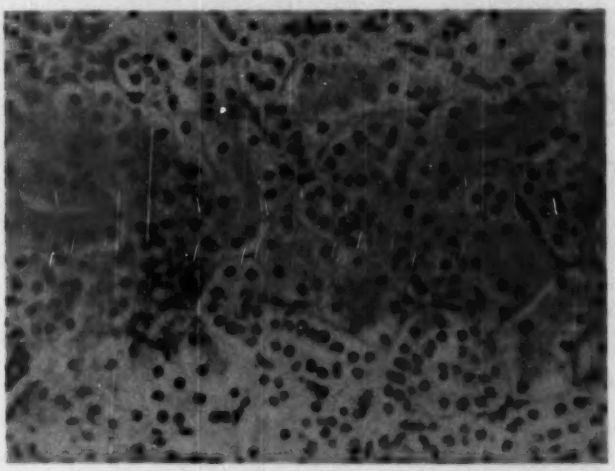

Fig. 2 (case 1).—Renal tubular epithelial cells showing fatty infiltration. Hematoxylin and eosin; × 320.

The cytoplasm of the vacuolated cells stained pale orange with scarlet red and light pink to pale violet with nile blue. Unstained hepatic tissue examined with polarized light showed the cytoplasm of the hepatic cells slightly refractile, especially at the periphery of the cell. Staining by the periodic acid Schiff method[7] revealed many red granules in the reticuloendothelial cells of the sinusoids; none were observed in the hepatic cells. Hematoxylin and eosin staining revealed no cytologic differences in sections cut from frozen or from paraffin-embedded blocks.

The renal glomeruli, blood vessels and interstitial and pelvic tissues showed nothing abnormal. The epithelial cells of the proximal and distal convoluted tubules, particularly those of the former, were swollen, though their inner borders were

7. McManus, J. F. A.: Nature, London **158**:202, 1946.

even and distinct (fig. 2). The cytoplasm of these cells showed considerable perinuclear and subnuclear vacuolation. There was similar, though more abundant, vacuolation of the epithelial cells lining Henle's loops. In many of the latter cells the nuclei were pyknotic or fragmented. Minimal perinuclear and subnuclear vacuolation was observed in the epithelial cells of the collecting tubules.

The cytoplasm of a few cells of the convoluted tubules, particularly of the distal group, contained brown pigment granules. Some tubular casts contained similar pigment. In frozen sections stained with scarlet red all the vacuolated cells contained fine, pale orange lipid droplets. These stained pink with nile blue. When viewed with polarized light, these lipid-containing portions of the renal parenchyma contained a few refractile amorphous crystals. Renal tissue embedded in paraffin and stained by the periodic acid Schiff method [7] showed no red-staining granules in the tubular epithelial cells.

The thymic lobules were greatly reduced in size. They consisted mainly of reticular tissue with numerous small Hassall's corpuscles. Comparatively few lymphocytes were present.

In numerous sections from all portions of the central nervous system there were no significant degenerative changes of the nerve cells. There was considerable pericellular and perivascular edema. Many of the oligodendroglial cells in the subcortical fiber tracts of the cerebrum and the cerebellum had swollen pale nuclei.

Case 2.—A. L., a sibling of K. L. (case 1), was a full term white boy who weighed 4,135 Gm. at birth. He was normal until the fifth day of life, when he began to vomit, and then fever, icterus and hepatosplenomegaly appeared. The presence of galactosemia and galactosuria and evidences of hepatic dysfunction were demonstrated. Elimination of milk from the diet caused regression of the clinical and laboratory signs of galactose intolerance. The clinical course and complete carbohydrate and other laboratory studies are to be published elsewhere.[1]

Eight days after exclusion of milk from the diet, a specimen of the liver was obtained for biopsy.

Biopsy.—Gross Examination: The specimen consisted of a 0.5 cm. block of pale, reddish brown hepatic tissue. There was no grossly evident scarring or granularity. Half of the block was fixed in dilute solution of formaldehyde U. S. P., and the other half was fixed in a formaldehyde-dioxane-picric acid-acetic acid solution [8]; both were embedded in paraffin.

Microscopic Examination: There was some variation in the size of the hepatic lobules, and their outlines were generally poorly defined except near the portal spaces (fig. 3*A*). The latter showed little histologic alteration. Their blood vessels were normal, and the supporting connective tissue was free of inflammatory reaction. The bile ducts were not dilated, and only a few of the smaller ones contained masses of bile pigment (figs. 3*B* and 4*A*).

Few of the hepatic parenchymal cells had the normal arrangement in cords (fig. 3*A*). The majority had a distinct alveolar grouping. Some of these epithelial cells surrounded biliary canaliculi, producing a distinct tubular pattern; these tubules often were distended with golden brown, inspissated, granular bile (figs. 3*A* and 4*A*). Other hepatic parenchymal cells surrounded a single hepatic

8. Lindsay, S.; Reilly, W. A.; Gotham, T. J., and Skahen, R.: Am. J. Dis. Child. **76**:239, 1948.

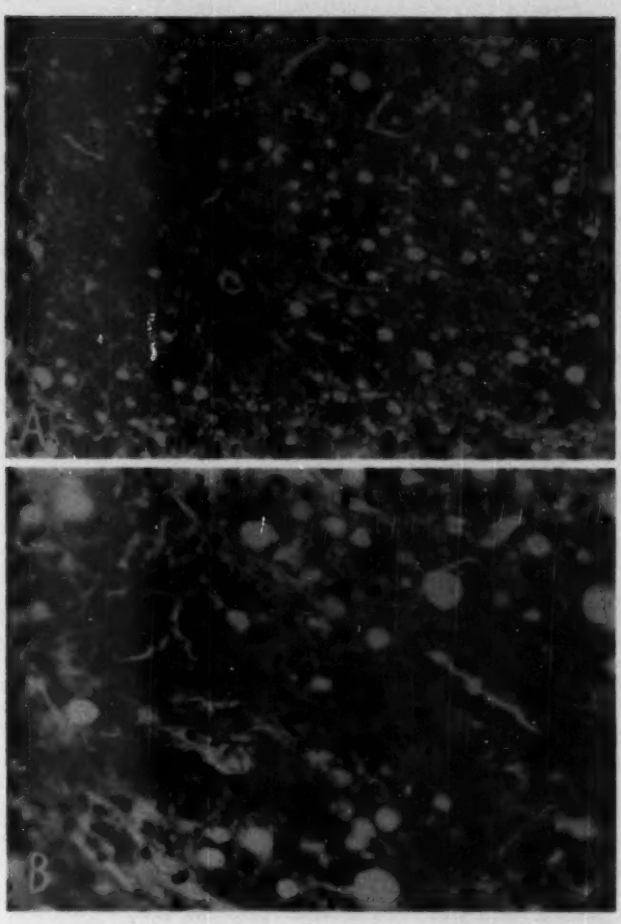

Fig. 3 (case 2).—*A*, liver showing distortion of lobules, irregular grouping of hepatic cells and increased prominence of collagenous stroma. Hematoxylin and eosin; × 160. *B*, liver showing intracellular lipid vacuoles and collections of neutrophilic leukocytes about degenerating parenchymal cells. Hematoxylin and eosin; × 320.

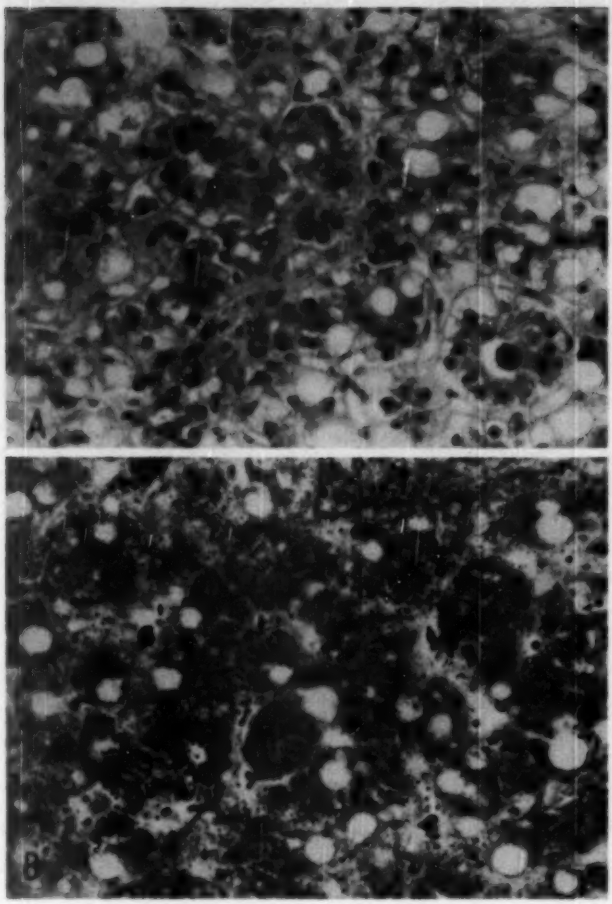

Fig. 4 (case 2).—*A*, liver showing alveolar and tubular grouping of many parenchymal cells. Hematoxylin and eosin; × 320. *B*, liver with abundant glycogen in many parenchymal cells. Many cells contain lipid vacuoles. Feulgen-Bauer stain; × 320.

cell containing a large lipid vacuole. Cellular groups of this type presented a pseudoacinous pattern (fig. 4 *A*).

The majority of the parenchymal cells were of normal size and had fairly uniform nuclei. Their cytoplasm was finely granular, vesicular and eosinophilic. Distinct cell membranes were usually present. Small light brown pigment granules were observed in a few cells. Fewer hepatic cells had more condensed, nongranular, homogeneous cytoplasm. Numerous parenchymal cells were distended by single large clear lipid vacuoles; these lipid-containing cells were distributed uniformly throughout the lobules (figs. 3 *A* and *B*, and 4 *A*).

Degenerative and reparative changes were present in this hepatic tissue. Single or small groups of hepatic cells were observed in various stages of degeneration or necrosis. Partially disintegrated cells were often surrounded by neutrophilic leukocytes (fig. 4 *A*). The disappearance of many hepatic cells that resulted from this destructive process was followed by collapse, condensation and edema of the supporting sinusoidal reticulum (fig. 3 *A*). This appeared as coarse branching collagenous bands when stained with Mallory's connective tissue stain. This material had mainly an intralobular distribution and often isolated small groups of epithelial cells. Coarse collagenous and reticular fibers lay in the periportal and interlobular areas as well. Evidence of actual proliferation of fibrous tissue was not observed. Numerous mitotic figures were seen in the parenchymal cells.

The continuity of the sinusoids was interrupted by the altered epithelial cells and condensed reticulum. These vascular channels contained little blood.

The large single vacuoles in the hepatic cells stained pale orange with scarlet red and pale pink with nile blue. Unstained sections viewed with polarized light revealed scattered small amorphous refractile granules in the lipid-containing areas. Those epithelial cells with finely vesicular cytoplasm did not contain fat, but when stained by the Feulgen-Bauer method[9] (formaldehyde-dioxane-picric acid fixation) they did contain abundant amounts of fuchsinophilic granular material, presumably glycogen (fig. 4 *B*). In the cells containing large lipid vacuoles, glycogen occupied the peripheral portion of the cytoplasm. A section that had been incubated with saliva at 37 C. for eighteen hours and then stained by the Feulgen-Bauer method still had considerable amounts of fuchsinophilic granular material in the hepatic cells.

COMMENT

Contrary to the most recent concepts[10] of the nature of the hepatic disease associated with galactose diabetes, the process is not one of abnormal or excessive storage of glycogen. The hepatic cells with centrally placed nuclei and abundant cytoplasmic glycogen[11] characteristic of glycogenosis and resembling vegetable cells were not observed in the livers of the 2 siblings described in this report. While glycogen was demonstrated in the hepatic cells of the second infant, the amount fell within the normal range both by chemical and by histologic determina-

9. Bensley, R. R., and Bensley, S. H.: Handbook of Histological and Cytological Technique, Chicago, University of Chicago Press, 1938, p. 105.

10. Mason and Andersen.[8] Mellinkoff, Roth and MacLaggan.[4]

11. Bridge, E. M., and Holt, L. E. Jr.: J. Pediat. **27**:299, 1945.

tion. In the livers of both infants the amount of fat was greatly in excess of the amount ordinarily seen in the liver in glycogenosis.

It is evident that the cause of the hepatic enlargement and dysfunction in these infants was a fatty infiltration of the parenchymal cells. From the clinical sequences it is apparent that the ingestion of galactose beginning at birth culminated in the deposition of fat in the hepatic parenchymal cells. It is possible that the relation of the disordered metabolism of galactose and the fatty condition of the liver in these infants is comparable to that in human or experimental diabetes mellitus in which for unknown reasons fatty infiltration of the liver may be associated with the abnormal metabolism of dextrose.

Comparison of the histologic and cytologic patterns in the livers of these 2 infants indicates clearly that the process is identical in both patients. However, in the second child the lesion was observed in a regressing stage, since for eight days before the biopsy was made milk had been excluded from the diet and the child was improving clinically.

The liver of the first infant, who died at the age of 8 days, showed pronounced fatty infiltration. Even though the deposits of fat presumably had been present only since birth, focal necrosis of hepatic cells and leukocytic infiltration had already occurred. The liver of the second infant also demonstrated active parenchymal cellular necrosis with acute inflammation. Numerous parenchymal cells had disappeared, allowing the supporting stromal framework to collapse and become condensed. While no active fibroblastic proliferation was observed at this period, this pathologic state was regarded as early cirrhosis. This early lesion might be expected to progress if the fatty infiltration persisted. At 9 months of age the infant described by von Reuss [8] had a pronounced cirrhosis.

Further comparison of the livers of the 2 siblings gave evidence of regression of the process. As judged by histologic methods there was less lipid in the parenchymal cells of the second infant. Although it was not possible to demonstrate glycogen in the liver of the first infant, the amount of intracellular fat present precluded the presence of significant amounts of glycogen. In the second infant's liver glycogen was present in normal amounts in most cells. Although there was considerable distortion of the hepatic lobules and of the arrangement of the cellular cords in the second sibling (the result of cellular necrosis and disappearance), regeneration as evidenced by considerable mitotic activity was observed.

If treated early by elimination of dietary galactose, this hepatic disease should be largely reversible. Conversely, delayed recognition and therapy would appear to lead to irreversible hepatic degeneration and

scarring. This complication, in addition to the possible development of cataracts, mental retardation and slowing of body growth, indicates the necessity for prompt diagnosis and treatment.

SUMMARY

Two cases of galactose diabetes occurring in siblings are presented. One sibling died at 8 days of age, and the second recovered when lactose was eliminated from the diet.

The hepatomegaly that occurs with galactose diabetes is the result of fatty infiltration of the liver. The secondary degenerative changes occurring in the hepatic cells may lead to hepatic cirrhosis.

MIXED TUMORS OF THE THYMUS

Criteria for Their Differentiation and Their Radiotherapeutic Response

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IT IS essential for the correct diagnosis of tumors of the thymus and for their differentiation from other mediastinal tumors, such as Hodgkin's disease and lymphomas,[1] that their dual ontogenetic origin be recognized.

The thymic epithelium develops from endoderm of the third branchial cleft. During the second fetal month this lobular epithelial reticulum becomes infiltrated with migrating lymphocytes of mesenchymal origin,[2] and the mixture of cells of these two types forms the thymus. The organ is known to reach full maturity at adolescence, after which regression begins. With this decline, neoplastic changes may begin. Both the cell types which make up the thymus may participate in the neoplastic processes. However, in certain cases the endodermal element takes the lead, and in other cases the mesenchymal element.

The varying proportion in which the two types of cells are present has led to a classification of thymic tumors according to the preponderant cell type in the tumor: (1) the carcinomatous group, (2) the lymphosarcomatous group and (3) the mixed group.

The carcinomatous group shows a preponderance of reticular epithelium with few lymphoid cells.

The lymphosarcomatous group,[3] in which there is a preponderance of lymphoid cells, is difficult to differentiate from lymphosarcoma elsewhere in the body, clinically or histologically, but on multiple sections some reticular epithelium may be found.

From the Departments of Radiology and Surgery, Medical College of Virginia.

1. Crosby, E. H.: Am. J. Cancer **16**:461, 1932.

2. (*a*) Bell, E. T.: A Textbook of Pathology, ed. 4, Philadelphia, Lea & Febiger, 1947, pp. 439-441. (*b*) Decker, H. R.: J. Thoracic Surg. **4**:445, 1935. (*c*) Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia & London, W. B. Saunders Company, 1941, pp. 997-1008. (*d*) Symmers, D.: Ann. Surg. **95**:544, 1932. (*e*) Crosby.[1]

3. Bomze, E. J., and Kershbaum, J. D.: J. Lab. & Clin. Med. **27**:928, 1938-1939. Craver, L. F., and MacComb, W. S.: Am. J. Cancer **16**:277, 1932.

The mixed group, in which both the reticular epithelium and the lymphoid series are represented in significant proportions, may be easily confused with Hodgkin's disease.[4]

Jones, quoted by Crosby,[1] stated that in mediastinal tumors the histologic resemblance to thymic tissue is one of the important diagnostic criteria. Decker [2b] showed that in thymic carcinoma the lymphocytes are comparatively few. Wilson and Pritchard [5] classified thymic tumors as lymphoblastic and reticular, depending on the type of the majority of the cells. They also stated that a histogenic analysis of the tumors classified as sarcoma reveals cellular tumors in which the cellular components range from small round cells, belonging to the lymphosarcoma series, to multilobed or multinucleated cells of the epithelial series.

Haagensen [4a] stated that the giant cells of mediastinal Hodgkin's disease "are different from those of Hodgkin's granuloma," and Ewing [2c] described reticular epithelium of the thymus developing into small round cells (thymocytes ?) difficult to differentiate from lymphocytes. Babès,[6] in his review of lymphoepithelial tumors, showed that nasopharyngeal lymphoepithelioma is merely epithelioma with a lymphoid stroma, whereas the only genuine mixed tumors are those of thymic origin.

MIXED TUMORS OF THE THYMUS

Histologically, in the mixed tumors of the thymus (figs. 1 through 6), as well as in Hodgkin's disease [7] (fig. 7), there is leukocytic pleomorphism; i. e., lymphocytes, plasma cells and eosinophilic and other cells of the granulocytic series occur. However, the mixed tumors, in general, tend toward a concentric type of fibrosis with formation of aborted Hassall's corpuscles. The multinucleated giant cells of mixed tumor of the thymus are two to four times the size of the Reed-Sternberg cells of Hodgkin's disease, and the reticuloepithelial cells of the former demonstrate a more clearly demarcated cell outline than the reticuloendothelial cells of the latter. Furthermore, their nuclei have coarser chromatin and their nucleoli tend to be somewhat larger and more prominently stained than those of the Reed-Sternberg cells of Hodgkin's disease.

The clinical manifestations of the two diseases may be very similar. Lymphadenopathy, particularly cervical, was a prominent finding in 6 of the 7 cases of mixed tumor of the thymus reported here. Only in 1 case was the neoplasm suspected of a primary mediastinal origin on clinical grounds alone. The nodes simulated those of a relatively early

4. (*a*) Haagensen, C. D.: Am. J. Cancer **16**:723, 1932. (*b*) Crosby.[1]

5. Wilson, F. H., and Pritchard, J. E.: Canad. M. A. J. **53**:444, 1945.

6. Babès, A.: Ann. d'anat. path. **6**:1105, 1929.

7. Jackson, J., Jr., and Parker, F., Jr.: Hodgkin's Disease and Allied Disorders, New York, Oxford University Press, 1947, pp. 3-112.

stage of Hodgkin's disease, being described as discrete, firm, nontender and nonpainful. The clinical symptoms, including fever, malaise, loss of weight and even pruritus in 1 instance, were of no differential assistance.

Roentgenologically, mediastinal widening was demonstrable in 5 of the 7 cases of mixed tumor of the thymus reported here, and in the remaining 2 the roentgenograms of the chest showed essentially normal conditions.

Control and palliation of the primary tumor and the metastatic foci was more satisfactory in the 4 cases in which fractionated high voltage roentgen radiation was used than in our cases of the fibrogranulomatous type of Hodgkin's disease,[8] although Burrows, reporting for Wyllie,[9] stated that roentgen radiation is ineffective in the treatment of thymic tumors. In 2 cases surgical removal of the mediastinal tumor was attempted, but in each instance it was incomplete. In our series the duration of life following the onset of symptoms ranged from forty to seventy months, with an average of 53.2 months. This compares with an average of 37.2 months (range, twenty to sixty months) for the cases of Hodgkin's fibrogranuloma previously reported.[8]

On the other hand, the ineffectiveness of nitrogen mustard in the treatment of mixed tumor of the thymus is suggested by the relative lack of response to this drug in 3 of our patients, one reacting adversely. In 2 of the patients treated with nitrogen mustard death occurred seven and twelve months after the onset of symptoms. The third patient when last heard from, ten months after the onset of symptoms (four and a half months after nitrogen mustard therapy was started), was in poor condition, with a steady downhill course and no significant response to the drug.

REPORT OF CASES

Case 1.—H. K., a 34 year old white woman, had had cervical lymphadenopathy for at least one year, and had been treated with roentgen radiation at another hospital after having received a diagnosis of Hodgkin's disease. More recent complaints included cough, fever, a sciatic type of pain and some numbness of the left arm and the right leg. There was also a recurring papular rash of the skin, with pruritus. Several groups of large, firm, discrete cervical, inguinal and axillary lymph nodes were noted. There was a questionable mass in the left midabdominal area, and the tip of the spleen was palpable. There was a papular dermatitis of the hands and arms and the trunk, with later pigmentation in these areas. Hirsutism was present. The patient's temperature chart during her stay in the hospital showed daily fluctuations between normal and 103 F.

A blood count showed 5,400,000 red blood cells—hemoglobin content 82 per cent—and 15,600 white cells, of which 76 per cent were polymorphonuclear leukocytes, 10 per cent lymphocytes, 6 per cent monocytes, 2 per cent eosinophilic

8. Sahyoun, P. F., and Eisenberg, S. J.: Am. J. Roentgenol. **61**:369, 1949.

9. Wyllie, W. G., cited by Burrows, N. F. E.: Proc. Roy. Soc. Med. **39**:591, 1946.

myelocytes and 6 per cent basophilic myelocytes. The urine was reported as showing many granular casts but was otherwise normal. Roentgen examination of the chest showed no evidence of pathologic changes.

Fractionated high voltage therapy was given on the basis of the biopsy report of Hodgkin's disease from another hospital. Over a period of four years the patient received 28,925 r (air) through multiple portals covering face, neck, thorax and trunk including the inguinal regions. The tumor responded well, with growth recurring at varying intervals, which also responded, but apparently the radioresponse gradually decreased. Death occurred approximately seventy months after the onset of symptoms.

Necropsy showed a mixed tumor of the thymus, which histologically exhibited the typical scattering of lymphoid cells, large tumor giant cells and reticular epithelium (fig. 1). There was an extensive spread involving lungs, pleura, liver, spleen, several vertebrae and all lymph nodes. Other findings included an adenoma of the cortex of the right adrenal gland, pituitary basophilism with Crooke's changes, a dermoid cyst of the right ovary and leiomyoma of the uterus.

Case 2.—L. T., a 36 year old Negro woman, had noted a small painless mass in her right posterior cervical region for two weeks. Examination showed this to be a fusiform, hard, fixed, nontender node measuring 4 by 2 cm. The results of the physical examination were otherwise essentially negative. The temperature chart showed only an occasional rise to 100 F.

Laboratory findings were essentially normal, and roentgen examination of the chest showed nothing of significance. Several months later, however, a moderate-sized upper mediastinal left-sided widening was demonstrable on a second roentgenogram. At this time the left half of the thorax was explored, but only incomplete removal of an anterior mediastinal tumor could be accomplished.

Histologic examination of the surgical specimen showed sheets of reticular epithelium with associated large tumor giant cells of mixed tumor of the thymus (fig. 2). Fractionated high voltage roentgen radiation was given over a period of two years, with total air doses of 600 r to the neck, 2,600 r to the mediastinum and 2,000 r to the right shoulder. Control of the tumor was temporarily satisfactory, with one remission of eight months after the first series of treatments, but with gradual decline and death at thirty-nine and a half months after the onset of symptoms.

Case 3.—H. S., a 28 year old white man, had noted swelling in the supraclavicular region for about one week, with cough productive of a small amount of sputum, which was blood streaked on one occasion only. Physical examination showed a large, rather soft, nontender mass in the left supraclavicular region.

The results of laboratory studies were essentially normal. A roentgenogram of the chest showed upper mediastinal widening measuring 18 cm.

Surgical exploration revealed the primary tumor to lie in the left anterior region of the mediastinum, and only incomplete removal was possible. During the following four years, fractionated high voltage roentgen radiation was given to the mediastinum and to various metastatic lesions, with total air doses as follows: chest, 5,500 r; left side of the neck and supraclavicular region, 7,850 r; right supraclavicular region, 6,400 r; skull, 4,200 r. Control of tumor and metastases was good, with surgical treatment and the original series of treatments causing regression of the mass for twenty-four months. Later recurrences showed gradually increasing resistance to irradiation, and the patient died five years after the onset of symptoms.

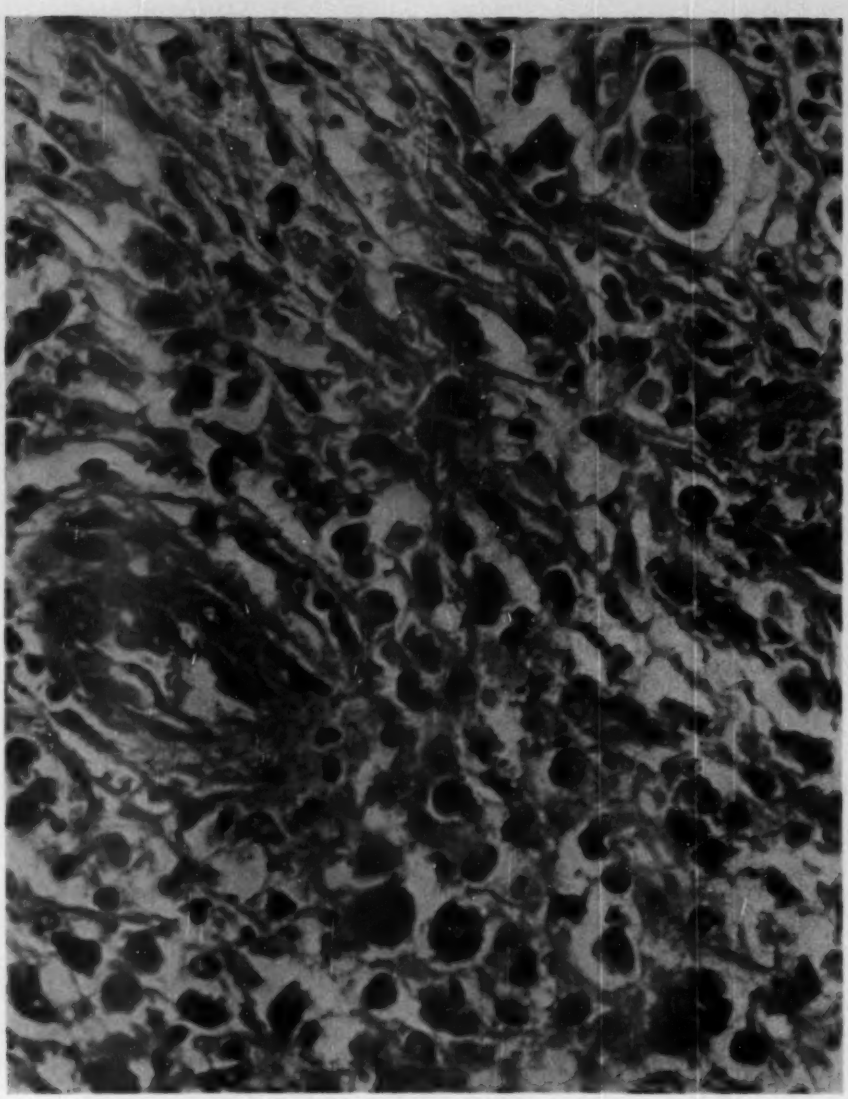

Fig. 1 (case 1.)—Mixed tumor of the thymus, which metastasized to all lymph nodes. Note the tumor giant cells and the reticuloepithelial sheets interlaced with some collagen fibers, and few lymphoid cells. A thickened arteriole, which is beginning to undergo fibrosis, is seen. Hematoxylin and eosin stain; × 765.

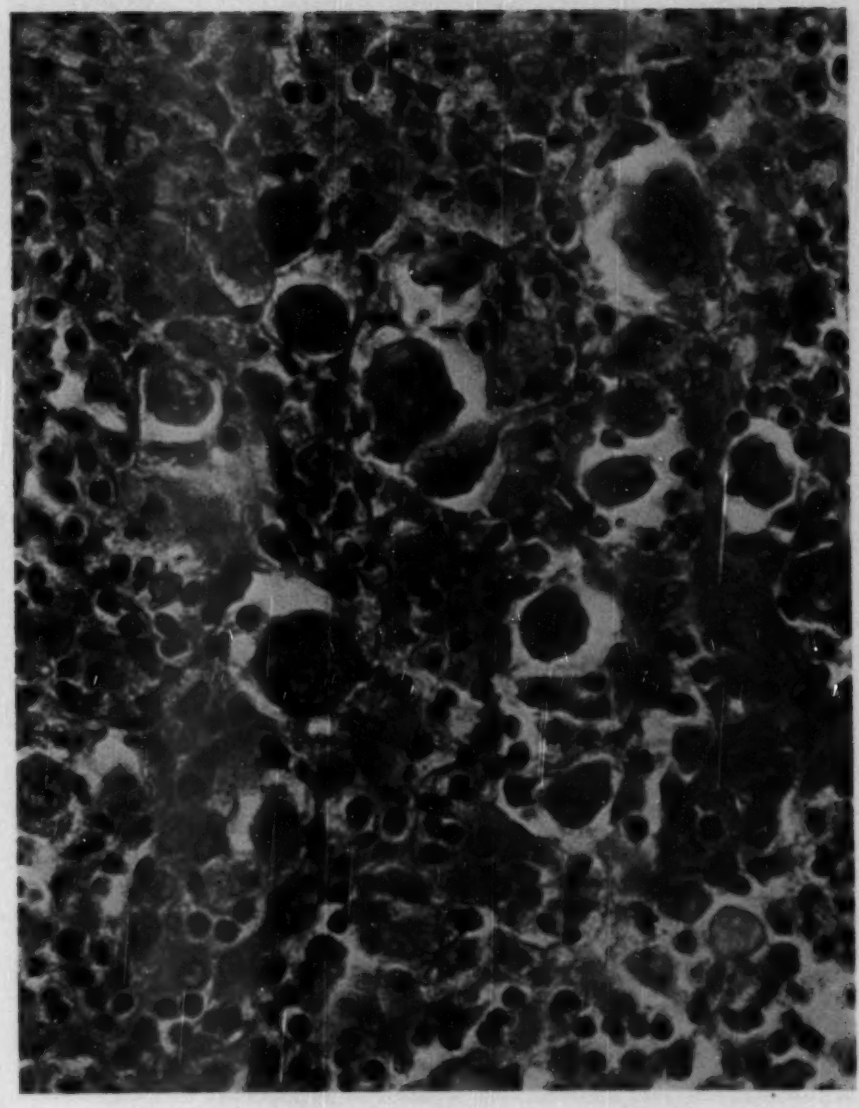

Fig. 2 (case 2).—The most cellular part of the mixed tumor of the thymus with sheets of reticular epithelium merging into a group of tumor giant cells, suggesting that the latter are derived from the reticuloepithelial cells. Hematoxylin and eosin stain; × 765.

Autopsy and review of several biopsy specimens showed a mixed tumor of the thymus, with few lymphoid cells, reticuloepithelial cells, large tumor giant cells, a tendency toward concentric fibrosis and aborted Hassall's corpuscles. Metastases were present in the lungs and various lymph nodes throughout the body.

Case 4.—C. H., a 35 year old Negro man, gave a story of twelve months' duration of an intermittent enlargement of lymph nodes, particularly of submental and axillary lymph nodes, with some pain but no tenderness. On examination there were moderately enlarged bilateral cervical and inguinal nodes. The laboratory reports were not remarkable, but moderate bilateral upper mediastinal widening was noted on roentgen examination of the chest. Biopsy of a cervical lymph node showed the mixture of lymphocytes, reticular epithelium and large tumor giant cells of mixed tumor of the thymus (fig. 3). Fractionated high voltage roentgen irradiation of the tumor was instituted, with air doses totaling 4,100 r to the neck, 3,550 r to the chest, 625 r to each axilla, 975 r to each inguinal region and 1,175 r to the abdomen over a period of thirty-one months. The primary tumor, the metastatic nodes and later the recurrent growths showed definite immediate response and later progressively increased resistance. Death occurred forty-three and one-half months after the onset of symptoms. Permission for autopsy was not obtained.

Case 5.—I. E., a 6 year old Negro boy, was admitted with a history of painless, nontender swelling of several left cervical nodes, moderate loss of weight and fever. The patient was pale, lethargic and slightly icteric, with a temperature of 103 F. and a pulse rate of 120. The cervical lymph nodes were enlarged, measuring in all 6 cm. in diameter. There was a blowing systolic murmur at the apex of the heart. The edge of the liver was 3 cm. below the costal margin, and the splenic tip was just palpable. There was moderate edema of the legs and scrotum.

The blood count showed 1,500,000 red blood cells—hemoglobin content 30 per cent—and 15,500 white blood cells, 45 per cent of which were lymphocytes and 55 per cent polymorphonuclear leukocytes, with a very rare myelocyte and a very rare normoblast, and 417,000 thrombocytes. The blood smear showed a hypochromic microcytic anemia with polychromasia, a slight shift to the left, toxic granules and occasional Döhle's inclusion bodies. The total serum protein was 6.5 Gm., with 2.8 Gm. of albumin and 3.7 Gm. of globulin. The urine was normal.

Roentgenograms of the chest showed a moderate upper bilateral widening of the mediastinum. Biopsy of a lymph node was interpreted, at first, as showing Hodgkin's sarcoma, and nitrogen mustard therapy was instituted. The first dose of 1.4 mg. of this drug was followed shortly by convulsions and coma, with death in thirty-six hours. Permission to make an autopsy was not obtained, but a critical review of the biopsy of the lymph node showed reticuloepithelial cells, tumor giant cells, aborted Hassall's corpuscles and scattered lymphocytes typical of mixed tumor of the thymus (fig. 4).

Case 6.—O. J., a 43 year old Negro man, had noted weakness, also pain in the back and thighs, for five months, with moderate loss of weight. On examination there was general lymphadenopathy, with the lymph nodes firm and discrete but nontender, the largest as much as 2 cm. in diameter. The spleen was palpable. Fever was rather constant, the temperature rising to 103.2 F. Laboratory studies gave essentially normal results.

A roentgenogram of the chest showed slight upper mediastinal widening. Biopsy of a cervical lymph node showed the mixture of reticuloepithelial cells, tumor giant cells and lymphocytes of mixed tumor of the thymus (fig. 5), and nitrogen mustard therapy was instituted. Two courses of four doses each were given, a total of 43.4 mg. There was decrease in the size of the lymph nodes for two and a half months;

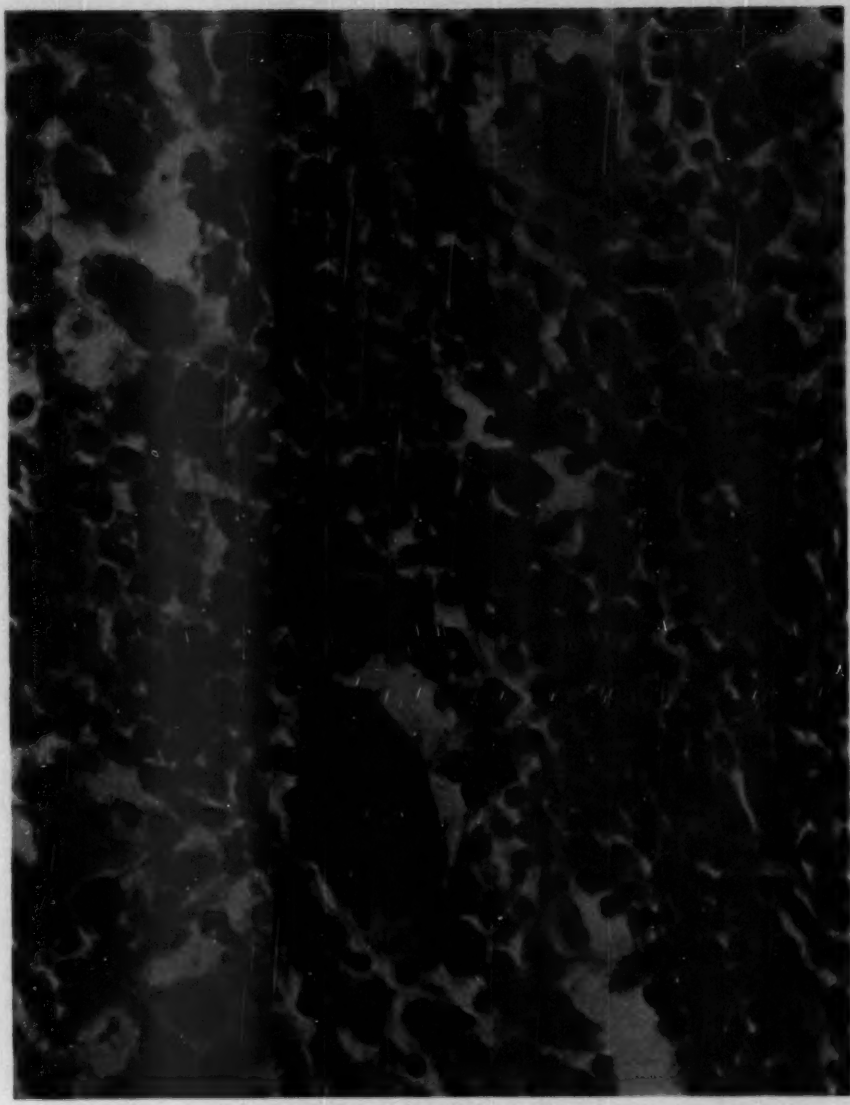

Fig. 3 (case 4).—Mixed tumor of the thymus showing the mixture of lymphocytes, reticuloepithelial cells and tumor giant cells. The latter differentiate this tumor from Hodgkin's disease, with which it may be confused. Hematoxylin and eosin stain; × 765.

Fig. 4 (case 5).—Mixed tumor of the thymus showing reticuloepithelial cells and tumor giant cells merging into an aborted Hassall's corpuscle. Lymphocytes are scattered throughout the field. Hematoxylin and eosin stain; × 765.

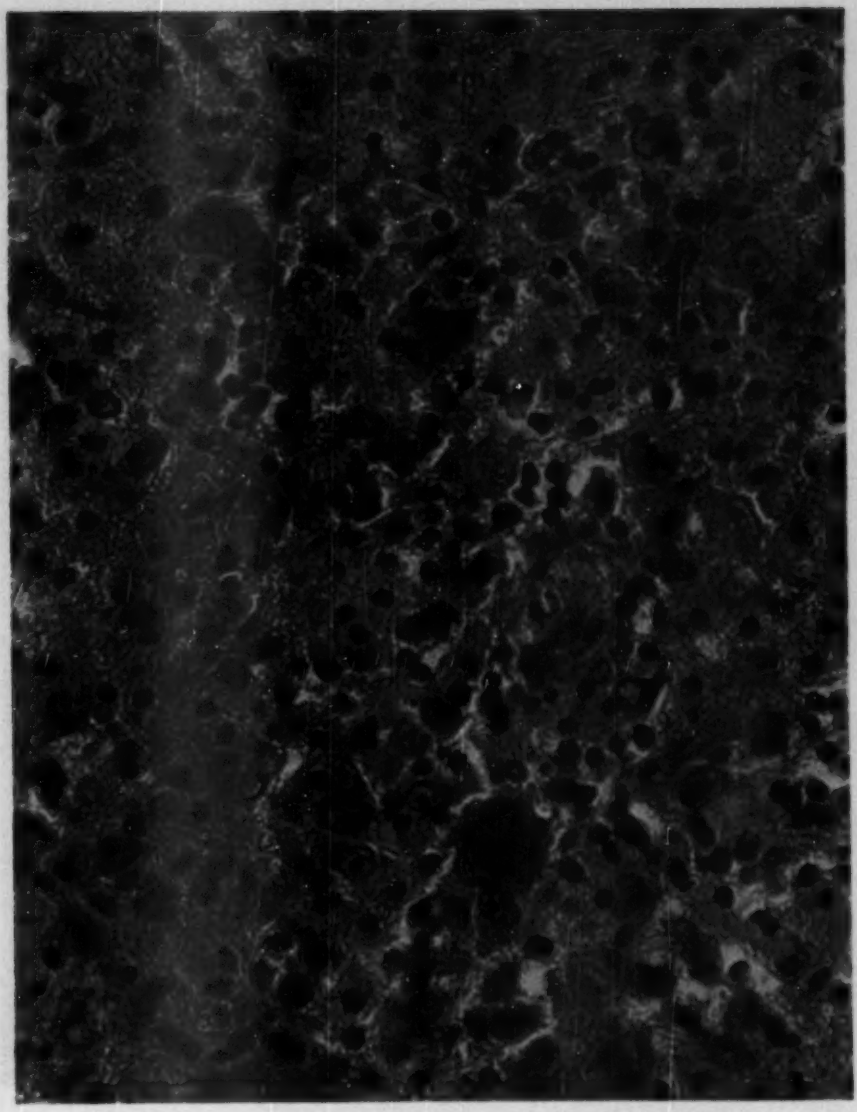

Fig. 5 (case 6).—Mixed tumor of the thymus showing the mixture of reticulo-epithelial cells, tumor giant cells and lymphocytes before treatment. Hematoxylin and eosin stain; × 765.

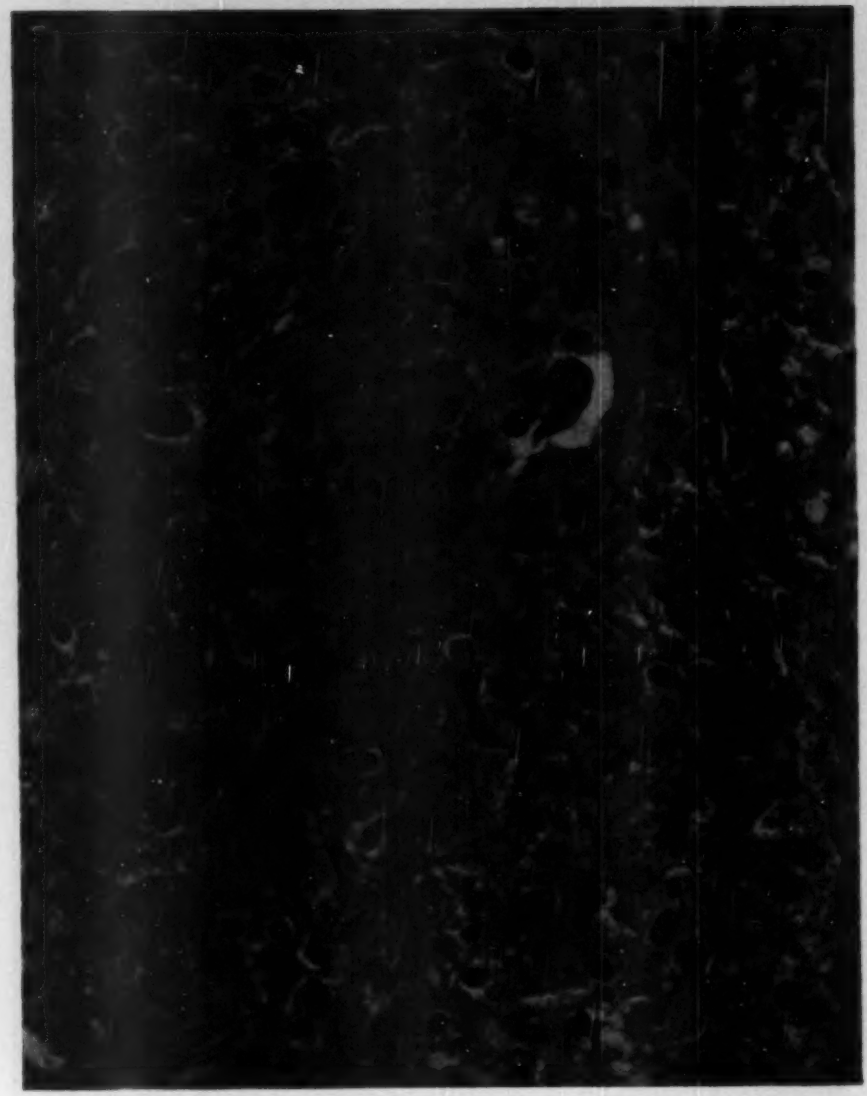

Fig. 6 (case 7).—Mixed tumor of the thymus showing reticuloepithelial cells, tumor giant cells, few lymphocytes and a tendency toward concentric fibrosis. Hematoxylin and eosin stain; × 765.

then the general adenopathy recurred, and there was a small mass in the right lumbar region with roentgen evidence of invasion of the twelfth dorsal and second and fifth lumbar vertebrae. A second biopsy showed the destructive effect of nitrogen mustard on the lymphoid element, with the reticuloepithelial cells relatively intact. The patient was last seen ten months after the onset of his symptoms and was in poor physical condition.

Case 7.—W. M., a 35 year old white man, complained of intermittent fever, sweating, headaches, malaise and weakness for a period of five months. On examination there were palpable cervical, inguinal and epitrochlear nodes. The liver and the spleen were palpable at the costal margins. During the patient's stay in the hospital his temperature chart showed an undulating type of curve, rising as high as 104.6 F. for about one week and then remaining normal, or almost so, for two to three weeks.

A blood count showed 3,600,000 red blood cells, the hemoglobin content 70 per cent. The white blood cell and thrombocyte counts were normal. Serum agglutination tests were positive for Brucella in dilutions to 1:160. The urine showed 8 to 10 white blood cells per high power microscopic field, with rare granular casts. Roentgen examination of the chest showed moderately enlarged hilar nodes.

Biopsy of a lymph node showed reticuloepithelial cells, tumor giant cells, a tendency toward concentric fibrosis and very few lymphocytes—diagnostic of mixed tumor of the thymus (fig. 6). The patient received four courses of nitrogen mustard therapy over a period of six months, totaling 96 mg. There was some improvement after the first course, but the neoplasm recurred within one month. Succeeding courses elicited even less response, with gradually increasing anemia and leukopenia. The patient died approximately one year after the onset of his symptoms.

COMMENT

Through its dual ontogenetic origin, namely, reticuloepithelium from the endoderm and lymphocytes from the mesenchyme, the thymus is capable of giving rise to thymic carcinoma and lymphosarcoma. These two disease entities have been accepted generally. However, only Babès [6] called attention to the possibility that mixed tumors may originate in the thymus, while Haagensen [4a] noted that the giant cells of mediastinal Hodgkin's disease are different from the giant cells of Hodgkin's disease elsewhere.

During our study of Hodgkin's disease [5] we found 7 cases in which the histologic picture did not conform with the standards we set for any of the different types of Hodgkin's disease. Further study of these showed a mediastinal mass in every case. Moreover, their course and irradiation response were not in accord with those of Hodgkin's disease. The differences may be summarized as follows:

1. Microscopic Appearance. Whereas the reticuloendothelium is a syncytial mass, the reticuloepithelial cells have definite cell membranes and finely granular, rather pale, uniformly staining cytoplasm. Their nuclei are rather larger than the reticuloendothelial nuclei, with coarser chromatin and very prominent nucleoli. The tumor giant cells are two to four times the size of the Reed-Sternberg cells and their nuclei

Fig. 7.—Hodgkin's disease [9] for comparison, showing the lymphogranulomatous pattern of reticuloendothelium, Reed-Sternberg cells, and the various types of leukocytes. Hematoxylin and eosin stain; × 765.

have the same distinguishing features as the reticuloepithelial nuclei. Compare the photomicrographs in figures 1 to 6, illustrating mixed tumors of the thymus, with that in figure 7, illustrating Hodgkin's disease, all taken with the same technic and the same magnification.

2. Course. In general it can be said that the course is more prolonged than that of the average fibrogranuloma of Hodgkin's disease.

3. Radiotherapeutic Response. Whereas in Hodgkin's disease the involvement of the nodes and the tumor disappear completely, in the mixed tumors of the thymus there are arrest and improvement but not complete regression.

4. Dissemination. Whereas in Hodgkin's disease the lesions occur in preexistent lymphoid tissue, the mixed tumors have a tendency to behave like carcinoma and infiltrate the adjacent organs, namely, mediastinal structures and lungs.

SUMMARY

Mixed tumors of the thymus are discussed, with particular reference to the histologic pattern and the criteria by which they may be differentiated from Hodgkin's disease.

The differential histologic features of mixed tumor of the thymus are: the reticular-epithelial sheets, the enormous tumor giant cells, the tendency toward concentric fibrosis and the formation of aborted Hassall's corpuscles.

The course and the therapeutic responses observed in the 7 cases herein reported suggest the superiority of roentgen radiation over nitrogen mustard in control and palliation.

EVIDENCE FOR AN INFLAMMATORY BASIS OF CORONARY ARTERIOSCLEROSIS IN THE YOUNG

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CORONARY arteriosclerosis is generally acknowledged to be a disease of the older age groups, but within recent years increased familiarity with its manifestations has led to its being recognized in a growing number of relatively young persons. The material available at the Army Institute of Pathology at the end of World War II, for example, permitted Yater and his associates [1] to report 866 cases of this condition with 450 necropsies in which the patients were men ranging in age from 18 to 39 years. In many of these the vascular disease was essentially limited to the cardiac vessels. This distribution is unlike that usually encountered in older patients, though we are aware of the frequent lack of parallelism in severity between the arteriosclerosis of the coronary arteries and that of extracardiac vessels.

There has accumulated an enormous literature purporting to show a direct relation between dietary factors, cholesterol specifically, and arteriosclerosis.[2] It is true that cholesterol or atheromatous deposits may be and often are striking features of arteriosclerosis, but the more constant and widespread intimal lesions characterized by hyaline fibrous tissue without lipid accumulations should not be ignored. As a matter of fact, there is weighty evidence that the latter represent the basic lesions and the lipid-rich plaques a secondary development. Winternitz and his associates [3] have shown with histologic preparations and meticulously executed reconstructions that intramural hemorrhage may furnish

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From the Armed Forces Institute of Pathology.

1. Yater, W. M.; Traum, A. H.; Brown, W. G.; Fitzgerald, R. P.; Geisler, M. A., and Wilcox, B. B.: Am. Heart J. **36**:334; 481; 683, 1948.

2. Plotz, M.: J. A. M. A. **139**:623, 1949. Leary, T.: Arch. Path. **47**:1, 1949.

3. Winternitz, M. C.; Thomas, R. M., and LeCompte, P. M.: The Biology of Arteriosclerosis, Springfield, Ill., Charles C Thomas, Publisher, 1938.

the bulk of the cholesterol material in arteriosclerotic lesions. Their views were substantially confirmed by observations on the fate of intramural hematoma during a recent study of dissecting aneurysms of the aorta.[4] Experimentally, Wartman and Laipply[5] found that intimal sclerosis developed in association with nearly 30 per cent of artificially produced intramural hematomas. Atheroma did not develop in these lesions, but the authors observed that "this intimal sclerosis could not be distinguished from histologically similar lesions which occurred naturally in uninjected arteries and in control animals." It may well be, however, that in man there is a form of primary arterial disease, atheromatosis, resulting from intimal deposition of lipids, in which the lesions are much like those found in rabbits after the administration of cholesterol.

There is danger that wholesale acceptance of the view that arteriosclerosis is directly related to the intake of cholesterol may unjustifiably eclipse information regarding other well substantiated causative factors already attested to in the literature. Klotz[6] concluded from his experiments that not one but many factors may lead to intimal hyperplasia; these included infection, bacterial intoxication and increased arterial tension. Karsner and Bayless[7] summarized the evidence that rheumatic fever and infectious processes may be forerunners of coronary sclerosis. A similar relationship of streptococcic infections of the sinuses and intimal disease of the cardiac arteries was proposed by Jones and Rogers.[8] Healed lesions of thromboangiitis obliterans may be virtually identical histologically with those of severe arteriosclerosis.[9] Other forms of arteritis, for which there is experimental evidence to indicate a relation to hypersensitivity,[10] may culminate in the same fashion. Even infants are not immune to arterial lesions leading to intimal fibrosis. Though the cases reported by Stryker[11] and Hause and Antell[12] were characterized by calcific deposits in the elastica interna and reactive intimal fibrosis, there were other areas in which the mineralized and degenerated elastica had been absorbed, leaving the vessel considerably narrowed by cellular fibrous tissue. Only fatal instances of this unusual lesion have been reported to date, but it seems reasonable

4. Gore, I.: Pathogenesis of Dissecting Aneurysm of the Aorta, to be published.

5. Wartman, W. B., and Laipply, T. C.: Am. J. Path. **25**:383, 1949.

6. Klotz, O.: J. Exper. Research **12**:707, 1910.

7. Karsner, H. T., and Bayless, F.: Am. Heart J. **9**:557, 1934.

8. Jones, N. W., and Rogers, A. L.: Ann. Int. Med. **8**:834, 1935; Arch. Path. **45**:271, 1948.

9. Saphir, O.: Am. Heart J. **12**:521, 1936.

10. Rich, A. R.: Bull. Johns Hopkins Hosp. **71**:375, 1942. Rich, A. R., and Gregory, J. E.: ibid. **81**:312, 1947.

11. Stryker, W. A.: Am. J. Path. **22**:1007, 1946.

12. Hause, W. A., and Antell, G. J.: Arch. Path. **44**:82, 1947.

to believe that some patients with less severe vascular damage survive, and in that group the healed lesion cannot be distinguished from arteriosclerosis. Even the ordinary obliterative endarteritis commonly seen in vessels traversing an inflammatory zone acquires more than the usual significance in the heart because of the end artery character of the coronary circulation. Such changes affecting the intramyocardial coronary radicals were described in a recent study of the myocardium involved in subacute bacterial endocarditis,[13] but they may also be found in other forms of myocarditis now known to be more frequent than has been generally recognized.[14] The multiplicity of the conditions just enumerated and the uniformity of the end results produced on the coronary arteries or their branches suggest that arteriosclerosis is essentially a vascular scar. The likelihood of finding clues to the causation of the scar diminishes rapidly with its age, and for that reason pathologic examination of the lesions of diseased coronary arteries of young persons

Grouping of the Changes Observed in Coronary Arteries of Young Soldiers

Group 1		Group 2		Group 3		Group 4	
Case	AFIP Acc.	Case	AFIP Acc.	Case	AFIP Acc.	Case	AFIP Acc.
1	91140	4	87270	8	92505	11	90097
2	111854	5	89438	9	138737	12	139187
3	169045	6	113810	10	89675	13	96544
		7	71594				

AFIP indicates Armed Forces Institute of Pathology.

would seem to offer the best opportunity of deciphering the mechanism by which they are induced.

MATERIAL AND METHODS

It was with the thought of assaying the importance of such factors in unselected material that we restudied the lesions of the cardiac vessels of 13 young patients who had died suddenly and unexpectedly of severe coronary heart disease. They were all male soldiers ranging in age from 18 to 29 years; 8 were younger than 25. They were selected as a representative sample of the younger group in the series reported by Yater and associates.[1] The material available consisted of slides bearing sections from multiple blocks of the myocardium and of the major coronary arteries, stained with hematoxylin and eosin. In a number of cases slides stained by the Masson trichrome technic and frozen preparations stained with sudan III were also available.

On the basis of the microscopic study of the changes occurring in the coronary arteries the cases could be divided into four groups, as listed in the table.

Group 1 comprised those cases (3) in which there was no evidence of inflammation either in the adventitia of the major arteries or in and about the smaller

13. Saphir, O.; Katz, L. N., and Gore, I.: The Myocardium in Subacute Bacterial Endocarditis: A Morphologic and Electrocardiographic Study, to be published.

14. Gore, I., and Saphir, O.: Am. Heart J. **34**:827, 1947.

intramyocardial radicals. If the large coronary arteries showed changes suggesting that the sclerosis they exhibited represented a late phase of an inflammatory condition, the cases (4) were placed in group 2. Three cases in which changes disclosed in the small intramyocardial arteries could not be attributed to any inflammatory process in the larger proximal segments of these vessels were placed in group 3. Finally there were 3 cases, constituting group 4, in which the coronary vessels combined the features characterizing groups 2 and 3.

Group 1.—In the 3 cases of this group the coronary lesions were limited to the major subdivisions of the two arteries. Microscopically, they were characterized by eccentric thickening of the intima due to the presence of hyaline fibrous tissue, which produced considerable narrowing of the lumen and secondary atrophy and displacement of the media. Varying amounts of fat, contained in macrophages, and a few lymphocytes were observed in the depths of the intimal plaques. The myocardial changes were entirely secondary to the vascular disease and are described in detail in the report of Yates and associates.[1]

Group 2.—In these 4 cases the lesions of the coronary vessels were limited to the larger arteries. In addition to the eccentric intimal hyaline and fibrous thickening observed in group 1 there were perivascular and adventitial changes of an inflammatory character, which histologically appeared to antedate the alterations of the adjacent media and intima. Allowing for minor individual variations, we may say that in each case the features of the disease were virtually identical with those in the other cases. They consisted of severe adventitial fibrosis, prominence of the vasa vasorum, which were frequently outlined by loose collars of histiocytic cells and lymphocytes, and endarteritis affecting the vasa to a varying degree. In case 7 the perineural sheaths of fortuitously included segments of cardiac nerve also exhibited dense fibrous thickening. A circumscribed, knoblike intimal plaque was observed at the point of exit of a small coronary radical, where, curiously enough, the adventitia was considerably thickened with fibrous tissue (fig. 1).

Group 3.—In these 3 cases careful microscopic examination of the large coronary arteries failed to reveal changes which, as in the last group, suggested an inflammatory process antedating the intimal disease. Significant lesions were observed, however, in the intramyocardial branches. In many respects the affected vessels virtually duplicated those observed by Gross, Kugel and Epstein[15] in chronic rheumatic heart disease. They were characterized by thick walls that exhibited concentric perivascular fibrosis, scarring and hypertrophy of the media, and narrowed lumens that frequently were lined by hyperplastic endothelium; essentially, they represented the healing or healed phase of arteritis (fig. 2 *A*, *B* and *C*). A few inflammatory cells (lymphocytes, eosinophilic granulocytes and histiocytes) were to be found, evidently the residue of the earlier, more cellular process; but in no case were there Aschoff nodules. The slight nodular thickening along the line of closure of the mitral valve in case 9 was consistent with a previous episode of rheumatic heart disease. In another of these cases (8) areas of myocardium exhibited an increase of connective tissue and a scanty collection of eosinophilic granulocytes and lymphocytes—a lesion compatible with resolving myocarditis (fig. 2 *D*).

Group 4.—In the 3 cases of this group the large coronary vessels and their intramyocardial branches presented lesions identical with those in groups 2 and 3, already described. In case 11 there was also a bicuspid aortic valve of the

15. Gross, L.; Kugel, M. A., and Epstein, E. Z.: Am. J. Path. **11**:253, 1935.

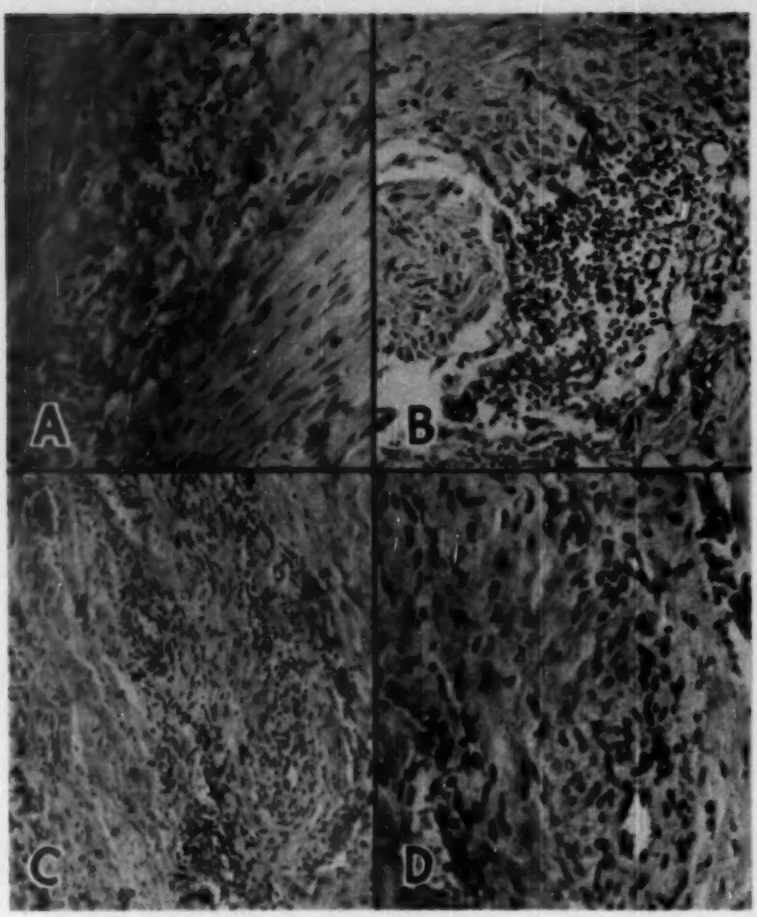

Fig. 1.—*A* (case 4), adventitia and media of a large coronary artery, showing adventitial fibrosis, vascularization and lymphocytic infiltration. Armed Forces Institute of Pathology Accession 87270. × 155. *B* (case 12), perineural fibrosis and lymphocytic infiltration adjacent to a large coronary artery. Acc. 99344. × 165. *C* (case 4), adventitia of a large coronary artery with abundant fibrosis and striking endarteritis of the vasa vasorum. Acc. 87270. × 125. *D* (case 4), detail of an adventitial vasa of a large coronary artery, exhibiting obliterative endarteritis. Acc. 87270. × 240.

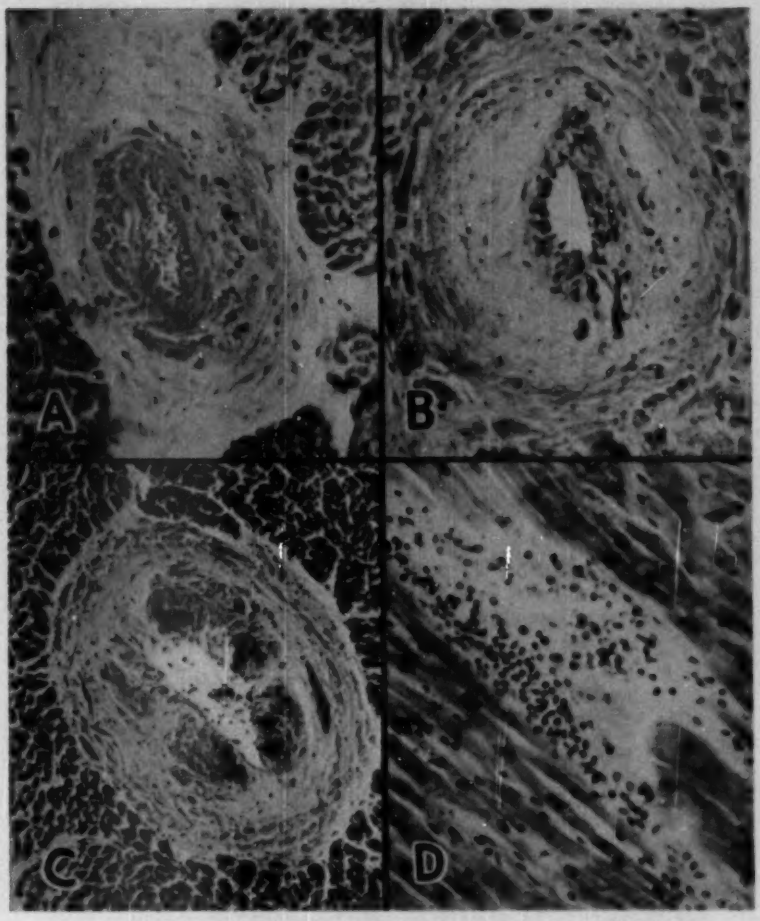

Fig. 2.—*A* (case 11), intramyocardial branch of a coronary artery, exhibiting a moderate degree of perivascular fibrosis and slight but distinct mononuclear cell infiltration of the adventitia. Armed Forces Institute of Pathology Acc. 80597. × 185. *B* (case 10), old arteritis of an intramyocardial branch of a coronary artery. Acc. 89875. × 200. *C* (case 9), healed arteritis of an intramyocardial branch of a coronary artery. Acc. 152737. × 125. *D* (case 11), focal perivascular inflammatory infiltration within the myocardium. See *A*. Acc. 80597. × 165.

acquired type, but no Aschoff bodies were found within the myocardium to prove the rheumatic origin of the deformity. A second heart (case 12) presented focal interstitial deposits of lymphocytes and was clearly the seat of old myocarditis.

COMMENT

The best opportunity for the morphologist to elucidate the pathogenesis of human coronary sclerosis is furnished by a study of the arteries of young persons. In the older age groups the lesions are much less likely to be found in formative stages. Furthermore, they are so often distorted by hemorrhage, calcification, ulceration and/or thrombosis that it would be futile to attempt to distinguish the residue of an initial process from purely secondary phenomena. At a late stage of arteriosclerosis it is as impossible to ascertain its pathogenesis as it is to establish the nature of an injury by examining the scar long after the initial insult.

In this sample of 13 fatal cases of coronary heart disease, unselected except as regards the patients' youth, the severe sclerosis of the cardiac arteries, which was uniformly present, was associated in 10 cases with evidences of an old inflammatory process. When this involved the small intramyocardial arteries, as it did in 6 instances (groups 3 and 4), the resultant lesions were identical with those observed by Gross, Kugel and Epstein [15] in chronic rheumatic carditis. Other substantial evidence of a previous rheumatic infection was present only twice, and to explain the remaining cases we are forced to acknowledge that etiologically nonspecific inflammation, as well as forms of arteritis and periarteritis of hyperergic (not necessarily rheumatic) origin, can produce these vascular changes. In 3 cases (group 4) the residue of an old inflammatory process was seen in the adventitia of large coronary vessels, an observation which gives rise to the speculation that the intimal disease might be entirely a secondary development. In the 3 remaining cases (group 3) the large coronary arteries presented no features of an inflammatory nature in the few sections examined. It is possible, however, that the advanced stage of the intimal disease may have completely overshadowed these much less conspicuous changes. In this regard it will be recalled that Gross and his associates [15] considered that the vascular lesions they observed in chronic rheumatic heart disease merged imperceptibly with those of arteriosclerosis. Karsner and Bayless,[7] in much the same vein, concluded that rheumatic fever predisposed to fibrosis of the coronary arterial tree in early life, or to what appears to be precocious coronary sclerosis.

Detailed clinical histories, which might have revealed confirmatory evidence of a past infectious process, were not available. All of the patients, who were soldiers physically qualified for military duty, died suddenly and unexpectedly. Even rather complete anamneses have their

limitations, however. The historian may easily overlook or ignore as insignificant the common infections of the upper respiratory tract or may fail to elicit a history of sulfonamide medication. Both of these, fortunately rather rarely, have been shown to be associated with significant myocarditis which may be clinically obscure.[16] At autopsy, only 3 subjects presented inflammatory lesions which might have been related to those involving the coronary arteries: chronic valvulitis, presumably rheumatic, in 2, and an old pulmonary focus of tuberculosis in the third.

No involvement of intramyocardial vessels was observed in the 4 cases of group 2, but the major vessels were the seat of an adventitial inflammatory process which seemed more ancient than the intimal disease. In 2 of these cases the adventitial scarring, the prominence of the vasa vasorum, the perivascular cellular infiltrates and the endarteritis of the vasa were reminiscent of the lesions of syphilis, but the absence of other stigmas would make such a categoric diagnosis untenable.

Arteriosclerosis in the broad sense may be subdivided into arteriosclerosis proper and atheromatosis. In the former the principal lesions are fibrous, progressing to hyalinization and calcification; in the latter there are, in addition, significant deposits of cholesterol and necrosis, which may be sufficiently extensive to cause ulceration of the intima. Intimal fibrosis resulting from inflammatory involvement of a vessel would not include fatty deposits, at least initially, as Wartman and Laipply [8] have shown. The subsequent mural vascularization, demonstrated by Winternitz, Thomas and LeCompte [5] and by Leary,[17] makes them vulnerable to hemorrhage; in turn, the breakdown products of unabsorbed red cells form a mass which cannot be distinguished from, if it is not identical with, atheromatous material. It is interesting to note, therefore, that the atheromatous alteration of the coronary lesions observed in persons less than 30 years of age in the group described by Yater and his associates,[1] was significantly milder than that seen in patients of the fourth decade. The evidence indicates, then, that young persons with vascular disease of relatively short duration frequently exhibit intimal disease of the type that would be anticipated if it were initiated by inflammation. At a later period of life a greater proportion of the lesions contain significant deposits of cholesterol. It would be an error, however, to assume that such a relation, true of early lesions, would persist with continued survival, since time permits absorption, fibrous tissue replacement and/or calcification to reduce the lipid content of plaques once rich in this material.

16. Gore, I., and Saphir, O.: Am. Heart J. **34**:831, 1947. French, A. J.: Am. J. Path. **22**:679, 1946.

17. Leary, T.: Am. Heart J. **16**:549, 1938.

SUMMARY

In some instances of juvenile coronary artery disease causing unexpected death the vascular lesions observed in the heart were associated with the residue of an old inflammatory process. In 6 of 13 cases examined there were lesions of the small intramyocardial arteries of the type previously reported as characteristic of chronic rheumatic carditis, though other residua of rheumatic infection were observed in only 2. In 3 of these 6 and 4 of the remaining cases old inflammatory changes were present about the large coronary arteries, also. Inflammation involving arteries may result in reactive intimal thickening, which in its late stages cannot be distinguished from, if it is not identical with, arteriosclerosis. It is possible, therefore, that in these cases the vascular lesions may have been a consequence of a primary inflammatory process.

BASIC HISTOLOGIC LESIONS OF MAGNESIUM DEFICIENCY IN THE RAT

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AND
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SAN FRANCISCO

MAGNESIUM ion is an essential component of a large number of metabolically important enzyme systems.[1a] It is not astonishing, therefore, that magnesium deficiency causes serious physiologic disturbances and leads to a number of pathologic changes. The symptoms of magnesium deficiency of the rat have been reported in a number of publications.[1]

Microscopic examination of the tissues of magnesium-deficient rats has revealed histologic lesions in skin, kidney, cardiovascular system, liver and teeth.[2] Many of these lesions have been inadequately characterized; certain of those described seem quite nonspecific, and others appear to be due to other inadequacies in the experimental regimens, rather than to lack of magnesium itself.

In the present study we shall describe the lesions of a group of rats maintained on a complete synthetic ration believed to be adequate in all respects and deficient only in magnesium. The work has led to the observation of an extremely generalized lesion which is believed to be basic for the effects of magnesium deficiency.

This investigation was aided by a research grant from the Christian Breon Fund for Medical Research.

From the Divisions of Pathology and of Biochemistry, University of California Medical School, San Francisco and Berkeley, Calif.

1. (*a*) Greenberg, D. M., and Tufts, E. V.: Am. J. Physiol. **121**:416, 1938. (*b*) Brookfield, R.: Brit. M. J. **1**:848, 1934. (*c*) Duckworth, J.: Nutrition Abstr. & Rev. **8**:841, 1939. (*d*) Follis, R. H.: The Pathology of Nutritional Disease, Springfield, Ill., Charles C Thomas, Publisher, 1948, pp. 27-32. (*e*) Kruse, H. D.; Orent, E. R., and McCollum, E. V.: J. Biol. Chem. **96**:519, 1932. (*f*) Schrader, G. A.; Prickett, C. O., and Salmon, W. D.: J. Nutrition **14**:68, 1937. (*g*) Tufts, E. V., and Greenberg, D. M.: J. Biol. Chem. **122**:693, 1937. (*h*) Watchorn, E., and McCance, R. A.: Biochem. J. **31**:1379, 1937.

2. (*a*) Becks, H., and Furuta, W. J.: J. Am. Dent. A. **26**:883, 1939; ibid. **28**:1083, 1941; Am. J. Orthodontics **28**:1, 1942. (*b*) Klein, H.; Orent, E. R., and McCollum, E. V.: Am. J. Physiol. **112**:256, 1935. (*c*) Cramer, W.: Lancet **2**:174, 1932. (*d*) Barron, G. P.; Brown, S. O., and Pearson, P. B.: Proc. Soc. Exper. Biol. & Med. **70**:220, 1949. (*e*) Follis.[1d]

MATERIALS AND METHODS

The diet and the methods are those described previously [1g] with the exception that vitamins were supplied in synthetic form.

Twenty-five rats were used—22 experimental and 3 control animals.[3] The age of each rat at the time at which the dietary regimen was started, the duration of the regimen, the location of the lesions and the presence or the absence of renal obstruction are recorded in the table. All the experimental rats gained weight during the first week to ten days of the deficient diet, after which the weight curve took the form of a plateau and loss began. This is similar to the growth response previously described.[1g]

The diet had the following percentage composition: casein, 25; sucrose, 54; hydrogenated vegetable oil, 13; cod liver oil, 2.5; salt mixture, 5.5. The salt mixture was composed of the following salts: calcium carbonate, 15 Gm.; potassium phosphate, 20 Gm.; sodium chloride, 10 Gm.; magnesium sulfate, 6 Gm. (sucrose substituted in the experimental diet) and ferric ammonium sulfate, 3.5 Gm. Traces of iodine, cobalt, zinc, manganese and copper were added. The salts were recrystallized from distilled water before they were incorporated in the diet. The casein was repeatedly washed with distilled water, first with water containing a small amount of added glacial acetic acid and then with pure water until the wash water was virtually mineral free. To each kilogram of diet the following amounts of vitamin supplements were added: thiamine hydrochloride, 12 mg.; riboflavin, 12 mg.; pyridoxine, 5 mg.; choline chloride, 1,500 mg.; calcium pantothenate, 30 mg.; inositol, 100 mg.; folic acid, 20 mg.; para-aminobenzoic acid, 10 mg., and nicotinic acid, 10 Gm.

Each batch of diet was analyzed for total magnesium, and slightly less than 1 mg. per kilogram was found.

The rats (Long-Evans strain) were housed in individual screen-bottomed cages. The diet was supplied ad libitum, and distilled water was available at all times.

Animals were killed when found moribund or after a given period by exsanguination following induction of chloroform anesthesia, and tissues were placed in formaldehyde solution U. S. P. (1:10) and prepared for histologic study, hematoxylin and eosin being used for staining.

RESULTS

The results are summarized in the table.

Two distinct types of lesions occur in this group of animals. The first type is seen in all the experimental rats, being well developed in those examined after two weeks of the deficient diet. It appears as an inflammatory, necrotic focus about a small blood vessel. The minimal development is evidenced by a clustering of polymorphonuclear leukocytes about a small capillary (*A* to *D* in the figure). Among these cells are fairly numerous eosinophilic polymorphonuclear granulocytes. In other animals a minute focus of necrosis is seen in this location, with the same collection of inflammatory cells. In animals restricted to the

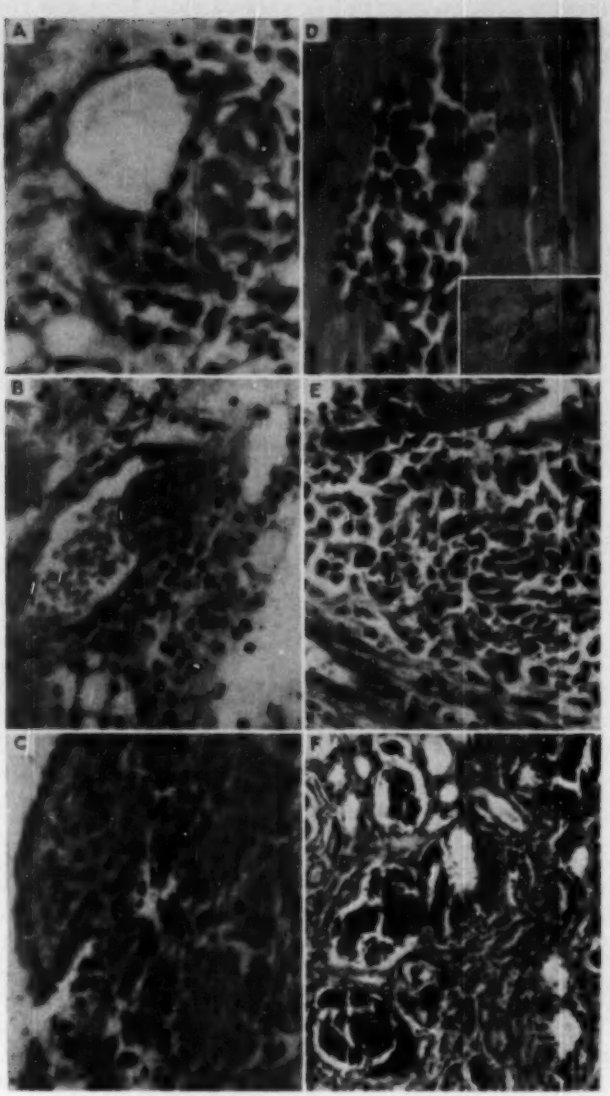
3. A large number of control animals was not considered essential, since adequate growth has been repeatedly demonstrated on this diet.

experimental diet for longer periods, scattered lesions of the acute variety just described may be seen, but in addition there are lesions which are marked by the presence of macrophages filled with pigment or debris

Data Concerning Rats Used in Study of Magnesium Deficiency

Rat	Age When Restricted to Magnesium-Deficient Diet, Days	Starting Weight, Gm.	Duration of Dietary Regimen, Days	Final Weight, Gm.	Location of Perivascular Lesion	Renal Obstructive Lesion
111	Mother	11	28	32	Very general: fat, skeletal muscle, myocardium, dermis	No
112	on diet	11	(7 days	29		
113	at birth of litter	11	after weaning)	31		
1154	3 days	..	14	50-56	Myocardium	...
1155	before weaning	..	..	50-56	Skeletal muscle, brain	...
1156	age (21	..	..	50-56	Fat generally	No
1158	days)	..	..	50-56	Myocardium, skeletal muscle	...
5	20	20	21	50	Myocardium	No
6	28	77	..	105	Myocardium, skeletal muscle	No
7	..	66	14	80	Skin	No
116	..	72	..	100	Skeletal muscle, cervical tissues, myocardium	No
118	..	..	..	116	Skeletal muscle	No
117	35	..	14	150	Pericardial fat, skeletal muscle, cervical tissue, myocardium	No
1159	..	51	40	74	Skeletal muscle, trachea	Yes
1162	20	42	56	60	Skeletal muscle	Yes
1163	..	41	..	100	Myocardium, skeletal muscle (old and new), fat, renal pelvis	Yes
1166	43	61	35	98	Skeletal muscle, skin, fat, esophagus	Yes
1160	47	53	26	78	Esophagus and trachea	Yes
1161	..	62	26	86	Myocardium and skeletal muscle	Yes
1165	37	66	42	126	Skin, muscle, fat, renal pelvis	Yes
1164	61	54	42	120	Skeletal muscle	Yes
			Controls			
112	Weaning	72	28	102	0	No
115	age (21 days)	70	28	213	0	No
1168	25	55	40	126	0	No

(figure, *E*). In other animals, fed the diet for still longer periods, both these varieties of the first type of lesion are noted and, in addition, areas in the same perivascular location and of similar size composed of fibroblastic tissue (figure *D* insert). Thus, it would appear that if the animal survives, this type of lesion undergoes an evolution, passing through an acute stage with perivascular inflammation to necrosis and then



Figures A-F

(See legends on opposite page)

through a stage in which macrophages remove debris to fibroblastic proliferation with scar formation. This is suggestive of the evolution of the skin changes described by Sullivan and Evans.[4]

Lesions of the type and varieties just described are extremely widely distributed, occurring in loose mesenchymal tissues throughout the body—that is, in practically every tissue examined. They are noted early in the dermis and the deeper subcutaneous fat. Quite regularly they occur in the loose cervical tissues about the wall of the esophagus and the trachea, lying in fat or in loose fibrous tissue. Mesenteric fat is another very usual site. An almost constant location is in the fibrous septums of skeletal muscle, both that of the extremities and that of the diaphragm. Two animals showed these lesions in adipose tissue of the renal pelves. The lesions were observed also in the central nervous system—illustrated in the wall of the lateral ventricle (figure, *C*).

The cardiac involvement deserves particular mention because of the interest of lesions in this location. Here the lesions follow the basic pattern established elsewhere. They occur in the subepicardial fatty tissue, about coronary radicals in the myocardium and in subendocardial tissue. In almost all the animals examined the lesions were found in the myocardium about small coronary radicals, often showing the various stages of evolution. These changes are illustrated in the figure, *D* and *E*.

The second type of lesion is evidenced by calcium casts in the distal portions of the convoluted and collecting renal tubules. About the casts

4. Sullivan, M., and Evans, V. J.: Arch. Dermat. & Syph. **49**:33, 1944.

EXPLANATION OF FIGS. A-F

A, acute perivascular inflammatory lesion of the fat of the renal pelvis. Many of the polymorphonuclear leukocytes are eosinophilic. Rat 1165, forty-two days of magnesium deficiency; hematoxylin and eosin stain; × 410. The same animal had organizing lesions in other locations.

B, acute inflammatory lesion about a vessel in the fibrous tissues of an intercostal muscle. Rat 118, fourteen days of deficiency; hematoxylin and eosin; × 320. Another lesion of the same animal is shown in *D*.

C, acute lesion of the wall of a lateral ventricle of the brain. Many polymorphonuclear leukocytes are present, as well as necrotic brain tissue and some macrophages. Rat 1155, fourteen days of deficiency; hematoxylin and eosin; × 320.

D, acute myocardial lesion, with presence of numerous polymorphonuclear leukocytes (some eosinophilic) and minimal necrosis. Rat 118, fourteen days of deficiency; hematoxylin and eosin; × 410. Insert: a late stage of the same type of lesion, showing a fibrous scar. Rat 1163, thirty-six days of deficiency; hematoxylin and eosin; × 320.

E, subacute stage of a lesion of the myocardium. A few polymorphonuclear leukocytes and many pigment-filled macrophages are present, and there is much fibroblastic proliferation. The lesion is located just beneath the endocardium. Rat 1161, thirty-six days of deficiency; hematoxylin and eosin; × 320.

F, renal lesion, evidenced by the tubular casts of precipitated calcium, about which there is a reaction of proliferated tubular epithelium. Rat 1159, forty-two days of deficiency; hematoxylin and eosin; × 160.

a foreign body reaction of the renal tubular epithelium occurs. This lesion is shown in the figure, *F*. It was not noted before twenty-five days of the experimental diet and occurs quite regularly after this period. This is shown in the table.

COMMENT

In the rat the basic lesion of magnesium deficiency appears to be an inflammatory reaction in loose mesenchymal tissues about blood vessels of precapillary and capillary size. With time it progresses from an acute stage with concentration of neutrophilic and eosinophilic polymorphonuclear granulocytes, through a necrotic stage in which macrophages appear, to a stage of fibroblastic proliferation and fibrous healing. It does not appear in all tissues simultaneously, as early and late phases may be seen in the same animal. The lesion is of much wider distribution than the acute dermatitis described by Sullivan and Evans.[4] The skin reaction which they described falls into the same general pattern and occurs in young rats within three or four days.[4] The myocardial and vascular lesion observed in calves [5] may well represent an end stage of the lesion described in the present study. The focal myocardial necrosis observed here is similar to that observed in the same location in potassium deficiency,[6] which, however, was not observed in general distribution. This perivascular lesion, the occurrence of which is so widespread, may well represent the anatomic basis of the increased capillary permeability suggested by Watchorn and McCance.[1b]

Recent studies [7] have shown a degenerative change in the Purkinje cells of the cerebellum in magnesium-deficient rats, chicks and rabbits. In the present study focal necrotic lesions of the same type found elsewhere, were observed in the central nervous system (figure, *C*). Since the convulsions of magnesium-deficient rats are transitory, it seems improbable that these necroses are etiologically related to them.

The renal lesion has received a great deal of attention.[8] In this study it required twenty-five days for the first calcium casts to appear, in contrast to the vascular lesion which occurred within two weeks. These casts are formed of calcium salts precipitated in renal tubules, the evolution of which has been described in chloride deficiency of the rat.[9]

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5. Moore, L. A.; Hallman, E. T., and Sholl, L. B.: Arch. Path. **26**:820, 1938.

6. Follis, R. H.; Orent-Keiles, E., and McCollum, E. V.: Am. J. Path. **18**:29, 1942.

7. Bird, F. H.: Nutrition **39**:13, 1949. Barron and others.[2d]

8. Greenberg, D. M., and Tufts, E. V.: J. Biol. Chem. **114**:xliii, 1936. Greenberg, D. M.; Lucia, S. P., and Tufts, E. V.: Am. J. Physiol. **121**:424, 1938. Cramer.[2c] Follis and others.[6]

9. Lowenhaupt, E., and Greenberg, D. M.: Arch. Path. **42**:49, 1946. Lowenhaupt, E.: ibid. **42**:572, 1946.

This is the lesion of the kidney of chronic alkalosis and of hypercalcemia.[10] Previous work[11] has indicated that serum calcium is not abnormal in magnesium deficiency. Magnesium ion has been shown to increase the stability of calcium in solution,[12] so that changes in the solubility of calcium salts in the renal tubule are not excluded. Neither are hydrogen ion changes in this region excluded. Watchorn and McCance[13b] have shown that late in magnesium deficiency of rats calcium is withdrawn from bone and teeth and excreted in urine and feces. In marantic animals the urinary concentration may likewise contribute to the development of this late lesion.

SUMMARY

An inflammatory lesion of extremely general distribution, involving loose mesenchymal tissues in perivascular locations, in the magnesium-deficient rat is described. This lesion occurs within two weeks in the young rat. In the early, acute stage it is evidenced by a collection of inflammatory cells; it progresses to necrosis and to scar formation if the animal survives. In addition, obstructive casts are found late in the deficiency in the distal portions of convoluted and collecting renal tubules, formed by calcium salts precipitated in this location.

10. Cooke, A. M.: Quart. J. Med. **2**:539, 1933.

11. Duckworth,[13c] Kruse and others,[13a] Tufts and Greenberg.[13d]

12. Greville, G. D., and Lehmann, H.: Nature, London **152**:81, 1943. Forbes, J. C.: J. Biol. Chem. **93**:255, 1931. Snyder, F. H., and Tweedy, W. R.: ibid. **146**:639, 1942.

CORONARY ARTERIOSCLEROSIS OF BIRDS

A Comparison of Spontaneous and Experimental Lesions

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ARTERIOSCLEROSIS occurs spontaneously in birds. The nature of the aortic lesion found in the domestic fowl varies with the portion involved. In this animal, the thoracic segment of the aorta is an elastic artery, whereas the abdominal aorta is a muscular artery. The spontaneous disease of the thoracic aorta, found mainly in female birds, manifests itself initially as an accumulation of lipids. In the abdominal aorta, on the other hand, the naturally occurring lesion is primarily fibrotic in nature and is observed most frequently in roosters.[1]

Lipemia of either exogenous (cholesterol feeding) or endogenous (injection of diethylstilbestrol) origin results in lipid infiltration of the arterial wall.[2] This lipid infiltration may cause a new atheromatous lesion or may modify a preexisting, spontaneous lesion. In the abdominal aorta, the deposited lipids become particularly abundant in the preexisting intimal fibrous plaques, which are apparently more susceptible to the permeation of lipids than are normal portions of the vascular wall. In the presence of either type of lipemia the rooster's thoracic aorta becomes the site of an atheromatous lesion resembling the one spontaneously occurring in the hen. Thus, the natural and the experimentally induced disease of the aorta are fundamentally similar but differ, essentially, in the amounts and proportions of the various lipids deposited.

In the cholesterol-fed bird the aortic deposition of lipid is but a single manifestation of the widespread storage of cholesterol and other

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1. (*a*) Dauber, D. V.: Arch. Path. **38**:46, 1944. (*b*) Chaikoff, I. L.; Lindsay, S.; Lorenz, F. W., and Entenman, C.: J. Exper. Med. **88**:373, 1948.

2. (*a*) Dauber, D. V., and Katz, L. N.: Arch. Path. **34**:937, 1942; (*b*) **36**:473, 1943. (*c*) Lindsay, S.; Lorenz, F. W.; Entenman, C., and Chaikoff, I. L.: Proc. Soc. Exper. Biol. & Med. **62**:315, 1946. (*d*) Horlick, L., and Katz, L. N.: J. Lab. & Clin. Med. **33**:733, 1948. (*e*) Chaikoff and others.[1b]

lipids. It is therefore not surprising that the lesion induced by administration of diethylstilbestrol resembles more closely the spontaneous lesion than does the lesion resulting from cholesterol feeding.

Previous observations in birds have indicated that both the spontaneous and the experimental forms of aortic and coronary arteriosclerosis begin in the intima.[3] When the media shared in the storage of lipid and in the growth of fibrous tissue, several investigators concluded that the medial disease was secondary to that of the intima. This concept of the genesis of arteriosclerosis of birds has been questioned recently by Paterson, Slinger and Gartley.[4a] They observed a high incidence of spontaneous and cholesterol-induced arteriosclerosis in the coronary arteries of cockerels.[4] From a study made with a serial section technic they concluded that the initial lesion was a focus of hydropic degeneration of the media and that this lesion antedated the formation of the intimal fibrous plaque.

Since the muscular coronary arteries and the abdominal aorta are similar in structure, a reinvestigation of the genesis of arteriosclerosis of the coronary arteries was undertaken.

METHODS AND MATERIALS

Three groups of birds, each consisting of 12 white leghorn cockerels aged 33 months, were used in this study. They had been reared on the low fat stock diet used in the division of poultry husbandry of the College of Agriculture (Davis), University of California.[1b] One group was given injections of diethylstilbestrol; a second was fed cholesterol; the third served as the control.

The details of the administration of diethylstilbestrol, the feeding of cholesterol and the diet of the normal control group have been described elsewhere.[1b]

The hearts were fixed in dilute formaldehyde solution U. S. P. A single block of tissue 0.5 cm. thick was removed just below the auriculoventricular groove. The block thus provided a cross section of both ventricles. Three contiguous frozen sections, 10 microns thick, were cut from the caudal surface of each block. One was stained with scarlet red and hematoxylin, and the second, with hematoxylin and eosin. The third section was examined, unstained, with polarized light. The rest of the block was then embedded in paraffin, and a fourth section from the same caudal surface was stained with hematoxylin and eosin.

RESULTS

Coronary Disease in the Control Group of Male Birds.—Nine of the 12 birds had an alteration in portions of the media of the coronary arterial branches which was the same as that described by Paterson, Slinger and Gartley.[4] In these portions the continuity of the medial muscular cells was interrupted by areas consisting of groups of cells

3. Dauber and Katz.[2a,b] Dauber.[1a] Lindsay and others.[2c] Chaikoff and others.[1b] Horlick and Katz.[2d]

4. (*a*) Paterson, J. C.; Slinger, S. J., and Gartley, K. M.: Am. Heart J. **35**:848, 1948; (*b*) Arch. Path. **45**:306, 1948.

showing vacuolation of their cytoplasm and apparent nuclear pyknosis (fig. 1 *A*). When, however, these muscular cells were examined in relatively thick sections, one saw that their nuclei were elongated, often folded, and resembled the nuclei of smooth muscle cells viewed on cross section or from their ends. Inflammatory cells were not present in these areas, and the adjacent adventitia showed nothing abnormal. In histologic and cytologic characteristics these portions of the media resembled, quite closely, cross section views of circular fibers of the normal artery (fig. 1 *B*). Lipid material was not found in these medial cells.

In 4 of the 12 birds a single small fibrous intimal plaque was found. The largest of the four plaques is illustrated in figure 1 *A*. One was found near a point of vascular bifurcation. Not one of these tiny plaques was found adjacent to a medial lesion of the type described in the foregoing paragraph. Lipids were not present in these small plaques.

Collections of chronic inflammatory cells were present in the myocardium of 8 of the 12 birds.

Coronary Disease in the Diethylstilbestrol-Treated Male Birds.—Focal areas similar to those described for the control group were found in the medial layers of the coronary arteries of 6 of the 12 birds studied. In 1 bird the media of half the circumference of one artery showed cellular vacuolation without nuclear pyknosis. These areas did not contain lipid material (fig. 2 *A*). In 3 birds, single small foci of adventitial fibrosis were observed; only one of these foci was adjacent to a medial zone showing mild cellular vacuolation (fig. 2 *B*), and this appeared to be near a bifurcation. Small intimal plaques of the type seen in the control birds were not observed in this group.

In 5 of the 12 birds, scattered lipid droplets were seen in the normal medial layers of a few arteries. The media was not otherwise altered, and cellular vacuolation was not evident. In an artery of 1 bird the inner portion of the media contained an oval hyaline mass which stained brownish orange with scarlet red. Numerous large lipid droplets were present in the adjacent media (fig. 3 *A*).

In the majority of the birds of this group there were fibrous thickenings of the ventricular endocardium and valves. The valvular connective tissue cells were swollen and vacuolated, and contained numerous lipid droplets. Macrophages were not present. No refractile material was seen in these areas when they were examined with polarized light.

Nine of the 12 birds had chronic inflammatory cellular collections in the myocardium. These were similar to those observed in the control group.

Coronary Disease in the Cholesterol-Fed Male Birds.—Seven of the 12 birds in this group had one or more myocardial arteries showing medial segments with the type of cellular vacuolation and nuclear

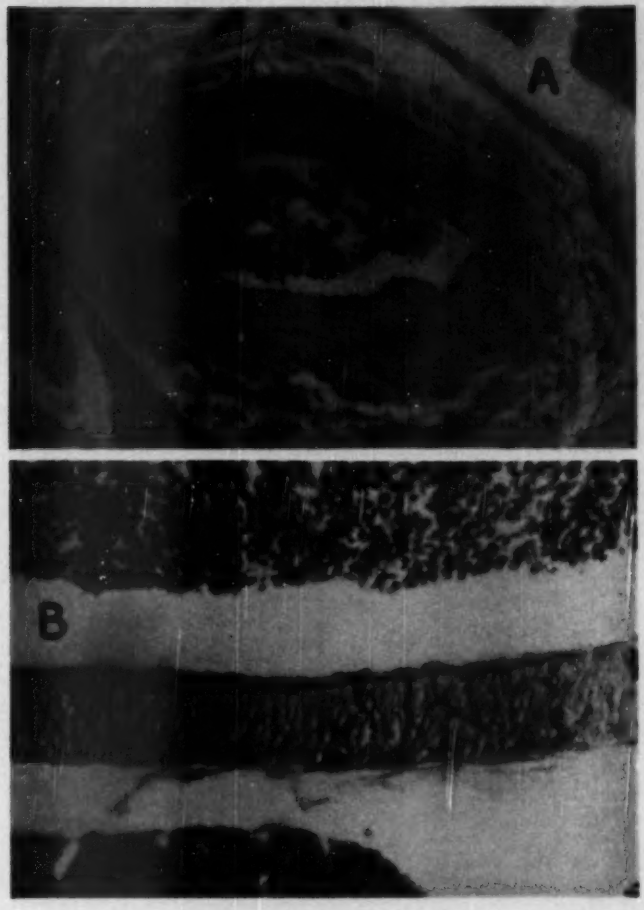

Fig. 1.—*A*, coronary artery showing cross sections of muscle fibers in the upper portion of the media and a small fibrous intimal plaque below; × 160; hematoxylin and eosin; control bird. *B*, longitudinal segment of a coronary artery showing circular muscle fibers cut transversely; × 160; hematoxylin and eosin; control bird.

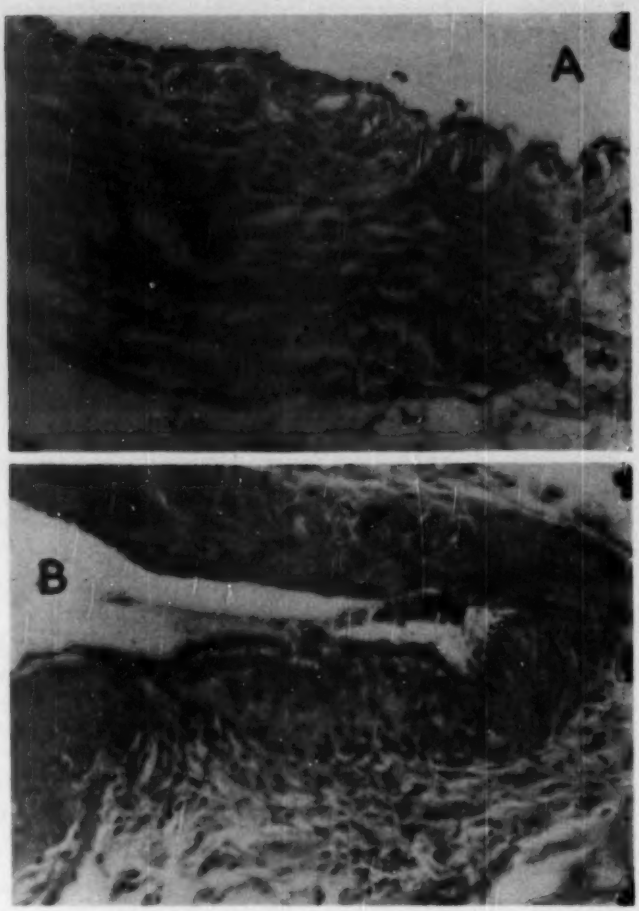

Fig. 2.—*A*, coronary arterial wall showing diffuse vacuolation of medial cells with absence of fat; × 320; hematoxylin and eosin; diethylstilbestrol-treated bird. *B*, adventitial fibrosis near a point of bifurcation; × 160; hematoxylin and eosin; diethylstilbestrol-treated bird.

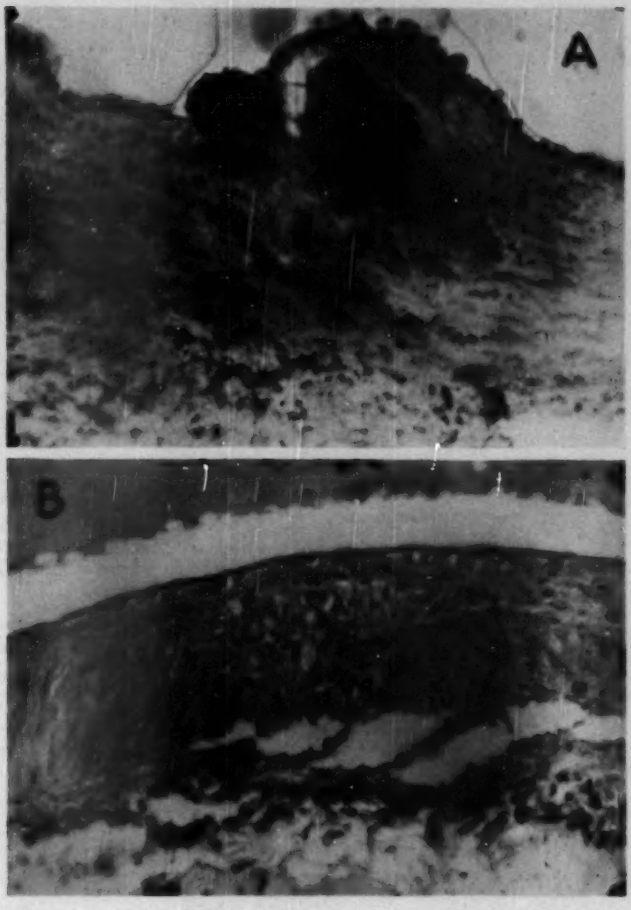

Fig. 3.—*A*, hyaline, lipid-containing mass and numerous lipid droplets in the medial layer; × 320; scarlet red; diethylstilbestrol-treated bird. *B*, coronary artery showing vacuolation of medial muscular fibers with absence of fat; × 160; hematoxylin and eosin; cholesterol-fed bird.

pyknosis described for the other two groups. Lipid material was not found in these medial foci (fig. 3 *B*).

Ten of the birds presented a variety of arterial, venous, interstitial, endocardial and valvular lesions in which lipid storage was evident.

Small veins and arteries often were almost occluded by masses of foam cells (fig. 4 *A*). In the small arteries the intima had been almost entirely replaced by the collections of foam cells (fig. 4 *B*), and it would therefore seem that the deposition of lipid was initially intimal. Medial atrophy or foam cell replacement appeared to be a secondary reaction.

The larger arteries often contained more extensive intimal plaques composed of fibrous tissue, which contained numerous foam cells. These larger plaques often projected through the media into the adventitia and appeared as nodular outpocketings (fig. 5 *A*). They often showed focal necrosis and, in addition, contained crystalline cholesterol and calcific deposits. At times these intimal deposits compressed the media.

In 1 bird a segment of the media of a single coronary artery was replaced by edematous, vacuolated, opaque, acellular tissue (fig. 5 *B*). This area showed lipids when stained with scarlet red and was refractile when viewed with polarized light. A thin layer of muscular tissue covered the lesion. The overlying intima was intact and normal. The lesion was distinctly different from the focal medial areas described in the foregoing pages.

Two other arteries in this group had deep medial lesions composed entirely of foam cells. There was no fibrous tissue or chronic inflammatory cells in these medial lesions. A thin layer of smooth muscle was seen above and below the medial plaque. The intima was of normal thickness and did not appear to be a site of lipid storage.

A coronary artery of 1 bird presented extensive foam cell alteration of the intima and, to a lesser extent, of the contiguous media. This lesion was further characterized by abundant calcific deposits in the deeper layers (fig. 6 *A*).

Some smaller coronary arteries had lipid droplets in the intima and the media without accumulations of foam cells, fibrosis or other alterations (fig. 6 *B*).

The foam cells observed in these vascular lesions were typical macrophages and did not resemble the fibroblastic foam cells previously described in the thoracic aortas of these birds.[1b] Scarlet red stained their cytoplasm a pale orange color. When viewed with polarized light, these cellular collections were found to contain moderate to large amounts of amorphous refractile material. In some of the larger vascular plaques, elongated fusiform crystals typical of cholesterol were observed.

Vascular involvement was only a part of the process of lipid storage in these cholesterol-fed birds. Groups of lipid-containing foam cells were often found in the pericardial fat and in the myocardial connective

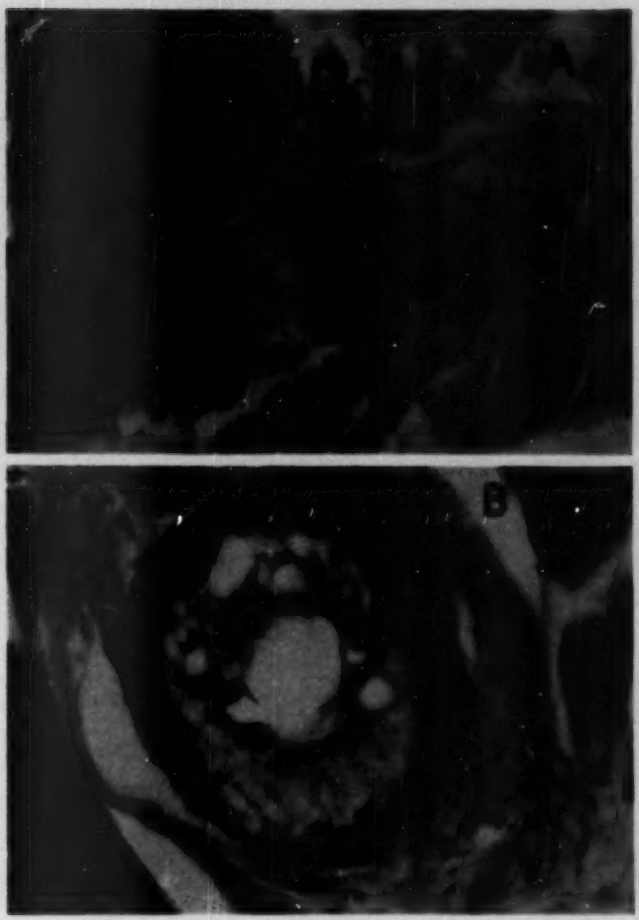

Fig. 4.—*A*, small coronary vein occluded by foam cells; × 160; hematoxylin and eosin; cholesterol-fed bird. *B*, coronary artery with thickened intima consisting of foam cells; × 160; hematoxylin and eosin; cholesterol-fed bird.

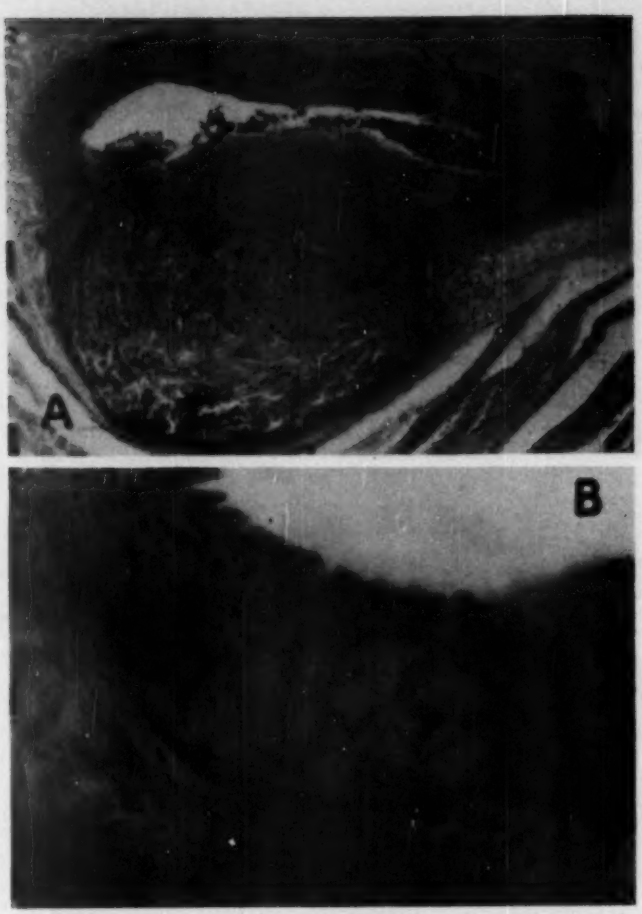

Fig. 5.—*A*, coronary artery with large atheromatous plaque projecting into the adventitia; × 80; hematoxylin and eosin; cholesterol-fed bird. *B*, coronary artery showing focus of medial vacuolation with contained lipid material; × 160; hematoxylin and eosin; cholesterol-fed bird.

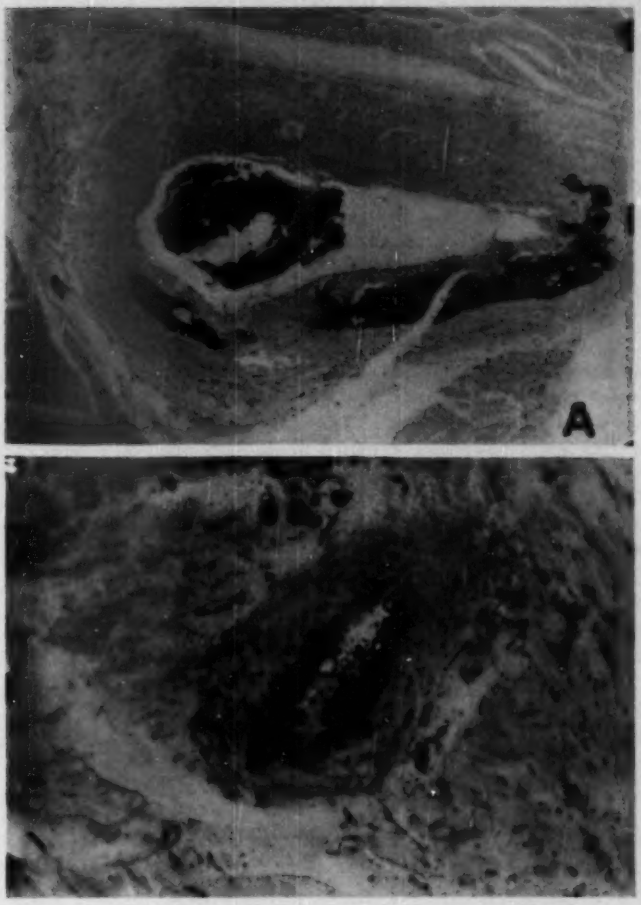

Fig. 6.—*A*, coronary artery with intimal and medial calcific deposits; × 80; hematoxylin and eosin; cholesterol-fed bird. *B*, small coronary artery with lipid deposits in the intima and the adjacent media; × 160; sudan IV; cholesterol-fed bird.

tissues. The endocardium and the valves showed abundant lipid deposited mainly in the swollen cytoplasm of the valvular and endocardial fibroblastic cells. Accumulations of foam cells containing lipid were often found in the endocardium and valves. Fibrocartilaginous metaplasia of a portion of the endocardium was also observed in 1 bird. This reaction was noted in the aortic intima of 1 bird of this group and has been noted previously.[1b]

There was considerable lipid (stained with scarlet red) in the lumens of the myocardial capillaries. Many minute lipid droplets were also present in the cytoplasm of the myocardial fibers. Some of this myocardial lipid appeared as fine, refractile particles when examined with polarized light.

Only 3 birds of the cholesterol-fed group showed chronic inflammatory cellular infiltration of the myocardium.

COMMENT

Various coronary arterial lesions have been described here. In the normal male birds the spontaneously occurring lesion consisted of a small fibrous intimal plaque which contained no lipid material. It was not associated with any significant alteration of the media. This minimal lesion was found in only 4 of the 12 normal male birds. It resembled closely the early spontaneous fibrous intimal lesion observed in the abdominal aorta in male birds.[1b] This early fibrous lesion was not found in the birds given injections of diethylstilbestrol or in those fed cholesterol.

In 6 of the 12 male birds given injections of diethylstilbestrol, lipid infiltration of the media without fibrosis or other alteration was noted. This medial deposition of lipid was similar to that previously observed in the abdominal aortas of some birds of this group.[1b]

The male birds fed cholesterol had a variety of cardiac lesions. In the arteries and the veins the infiltrating lipid lay within macrophages which occupied primarily the intima. When the foam cell plaques were large, they compressed or even replaced the medial layer. A few arteries contained lipid deposits, also within foam cells, but localized to the medial layer; in these arteries the intima appeared free of disease. Unlike the spontaneously occurring process, there was extensive deposition of lipid in veins, myocardial fibers and endocardium in these cholesterol-fed birds.

Paterson, Slinger and Gartley [4] described a medial degenerative lesion of the coronary arteries of normal male birds, consisting of focal areas showing nuclear pyknosis and hydropic cytoplasmic degeneration. These vacuolated muscular cells did not contain lipid. It was the belief of those authors that this focal medial lesion was the earliest manifesta-

tion of coronary arteriosclerosis occurring spontaneously in the normal bird and that it not only preceded the fibrous intimal plaque but resulted in the development of this plaque. Furthermore, they stated that when cholesterol is fed, lipid infiltration takes place first at these sites of preexisting medial degeneration and that intimal foam cell plaques represent extensions of the initial medial deposits.

The medial phenomena described by Paterson, Slinger and Gartley were also observed by us in 9 birds of the control group. Paterson, Slinger and Gartley failed to find these phenomena in their cholesterol-fed birds. But in the present study, not only the birds that had been fed cholesterol but also those that had received injections of diethylstilbestrol presented these medial lesions.

The muscular cells of the arterial media are generally circular but may occasionally lie obliquely or even longitudinally. When groups of smooth muscle cells are viewed on cross section or from their ends, the nuclei appear small and round. It has been pointed out that during postmortem contraction, some muscular nuclei undergo a spiral crumpling and contraction, with the chromatin tending to collect at the nuclear poles.[5]

The "hydropic" lesions of the media occurring in our three groups of birds have been interpreted as groups of muscular fibers viewed from their ends. It could often be demonstrated, in thick sections, that the nuclei in these areas were elongated and spiraled, and thus resembled nuclei of smooth muscle fibers. *A few normal arterial vessels which had been sectioned longitudinally showed this apparent nuclear pyknosis and hydropic cytoplasmic degeneration in the entire medial layer.* This condition was frequently localized near arterial bifurcation—points at which the muscular fibers do not have a distinct circular pattern. The occasional demonstration of tiny intimal fibrous plaques in association with the medial lesions is not remarkable, since intimal plaques of various sorts often are found at arterial bifurcations when they are not found elsewhere. These medial "hydropic" foci did not contain lipid substance. We have interpreted them as postmortem changes and we believe that they are not necessarily the sites of cholesterol deposition after feeding. Identical foci of "hydropic" muscle fibers are often seen in human and canine arteries.

The small intimal plaques found in the coronary arteries of the normal birds were of the same fibrous nature as the earliest abdominal aortic lesions. The coronary artery and the abdominal aorta are muscular arteries, and their spontaneously occurring intimal lesions differ from the lipid-containing intimal plaques found in the thoracic aorta, which is an elastic artery.[1b]

5. Bremer, J. L., and Weatherford, H. L.: A Textbook of Histology, ed. 6, Philadelphia, The Blakiston Company, 1944.

In the bird in which lipemia has been induced, lipid material may appear anywhere in the arterial wall, even in an otherwise normal vessel. This is particularly true in the case of a cholesterol-induced lipemia, in which the area of arterial involvement is only one site of a widespread storage of cholesterol and other lipids. In the hearts of cholesterol-fed birds, lipid deposits were found not only in the arterial walls but in veins, endocardium, valves, myocardial fibers and interstitial connective tissues. In the arteries this lipid may be stored either in normal intima or in thickened, fibrotic intima. Lipid deposits may also appear in the media alone, particularly when cholesterol is fed. Our observations that lipid deposits occur solely in the media in some vessels in cholesterol-fed birds are in agreement with those of Paterson, Slinger and Gartley.[4] But we believe that these medial lipid-containing lesions are the result of a widespread, nonselective deposition of lipid and do not represent lipid deposited at sites of preexistent degenerative medial disease.

SUMMARY

A comparison has been made between spontaneously occurring coronary arterial disease of birds and the lesions induced in the coronary arteries of birds by lipemias of endogenous origin (diethylstilbestrol injection) and exogenous origin (cholesterol feeding).

A spontaneous coronary arterial lesion in the form of a small intimal fibrous plaque entirely free of lipids was found in 4 of 12 control birds.

This spontaneous intimal lesion was not found in the diethylstilbestrol-treated birds. In these birds the coronary vascular lesions were confined entirely to the media and consisted of lipids only.

Various coronary vascular lesions were observed in the cholesterol-fed birds. Initial medial depositions were found in a few instances, but in the majority the disease appeared to be intimal in origin.

No evidence was obtained to support the view that a medial degenerative lesion precedes the appearance of intimal disease in the normal control, the diethylstilbestrol-treated or the cholesterol-fed bird.

IODIZED POPPYSEED OIL GRANULOMA

Report of a Case

H. C. FORTNER, M.D.
LOS ANGELES
AND
J. S. MILES, M.D.
CHICAGO

VEGETABLE oils with organically combined iodine (39 to 41 per cent) are used for such roentgenographic visualization as is required in bronchography and myelography. These preparations decompose when exposed to air and light. Lipiodol® N.N.R. is an organic combination of iodine and poppyseed oil. This is not a stable combination, as evidenced by the discoloration which appears in the ampul of this preparation which is outdated.

The reactions to the instillation of iodized popyseed oil noted in the literature may be divided into three categories. The first is that of anaphylactic shock and allergies. The second is that of iodism, which appears twenty-four to forty-eight hours after the introduction of the iodized oil. This, again, is due to dissociation of the poppyseed oil and the iodine. It is well known clinically that patients who swallow iodized oil are more prone to symptoms of iodism than those in whom the instillation is restricted to the respiratory tract. It is felt that this is due to more rapid dissociation of the iodine and poppyseed oil in the gastrointestinal tract. The third type of reaction is seen in pneumonia which develops two to ten days after the introduction of the oil. These are transient inflammatory reactions, well localized to those areas of the lung in which the oil is retained. They are characterized by fairly typical attacks of pneumonitis, with chills, fever and malaise. The attacks, in general, vary in severity with the amount of iodized oil retained.

The cases of granuloma due to iodized poppyseed oil reported in the literature are not numerous, but when articles are assembled dealing with reactions following injections and inhalations of radiopaque substances and petroleum products, they become impressive.

From the Veterans Administration Hospital, San Fernando, Calif.

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Iodized oils were first employed by Sicard and Forestier [1] to aid in location of obstructions of the spinal canal. Schneider and Segal [2] reported a case wherein oil was noted two years after instillation.

Pinkerton,[3] after studying the effects of vegetable oils introduced into the lungs of puppies and rabbits, concluded that no reaction was produced and that normal lungs or those free of infection were not injured.

The Report of the Council of the American Medical Association [4] lists several cautions, two of which are: First, oils that have aged and darkened beyond their original color should never be used; second, intratracheal and intrapleural injections should be avoided when there is tuberculosis of the respiratory organs and, also, when any restriction of the respiratory area would be contraindicated.

Wright,[5] reported a case of a patient having partial occlusion of the bronchus due to epithelioma, in whom lipiodol® was introduced twelve months prior to death. Distal to the occlusion the iodized oil was present in bronchiectatic cavities, shown in the roentgenograms and in the specimen. Microscopically, oil globules were found in macrophages within the alveoli of the lung distal to the occluded bronchus. There was no tissue reaction and no collagen formation.

Flamm [6] reported a case wherein the patient was given a single instillation of lipiodol® for nonseasonal asthma. Two years later, roentgenograms showed the shadows of deposits of iodized oil. Two years after that the patient died during a paroxysm of asthma. While there is no mention of necropsy, the author stated that he believed the pneumonitis and the retained oil, as shown by roentgenogram, were responsible for the continuous asthma which resulted fatally.

Rubin,[7] reported an iodized poppyseed oil granuloma in the fallopian tubes. Sections revealed caseating salpingitis resembling tuberculosis, but no tubercle bacilli could be found. The patient had received an injection of lipiodol® five months previous to the salpingectomy.

Marcovich, Walker and Jessico [8] listed among the late effects following intrathecal injection of lipiodol® mild arachnoiditis and adhesions of arachnoid and dura, but found no granulomatous tissue.

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1. Sicard, J. A., and Forestier, J.: Bull. et mém. Soc. méd. d. hôp. de Paris **47**:309, 1923.

2. Schneider, L., and Segal J.: Am. Rev. Tuberc. **35**:590, 1937.

3. Pinkerton, H.: Arch. Path. **5**:380, 1928.

4. Report of Council of the American Medical Association, J. A. M. A. **99**: 1946, 1932.

5. Wright, R. D.: Am. J. Path. **11**:497, 1935.

6. Flamm, G.: J. Allergy **9**:593, 1938.

7. Rubin, I. C.: Radiology **33**:350, 1939.

8. Marcovich, A. W.; Walker, A. E., and Jessico, C. M.: J. A. M. A. **116**: 2247, 1941.

Sheldon [9] reported 2 cases of long pulmonary retention of lipiodol® and speculated whether or not the iodine becomes fixed in bronchiolar tissues because of an allergy.

Brody [10] reported an instance of focal lipid granulomatosis of the lung following instillation of iodized poppyseed oil. His patient was a 52 year old white man with a neoplasm which partially occluded the right main stem bronchus. One month prior to surgical treatment of the patient, 10 cc. of lipiodol® was introduced into the right lung. The iodized oil did not penetrate the tumor area but filled the other portions of the right lung. In the lung, obtained by pneumonectomy, a polypoid tumor had formed a valvelike structure partially obstructing the bronchus of the lower lobe of the lung and, to a lesser extent, that of the middle lobe. Microscopically, these nodules consisted of tubercle-like structures, in the center of which were fat globules. Surrounding these lipid deposits, a fairly dense collar of collagen was seen. Brody [10] utilized special stains and concluded that the lipid deposits were retained iodized oil. Occasional fat-laden macrophages were found in lymphatic channels at some distance from these nodules. Roentgenograms of thin slices of the specimen showed tiny radiopaque areas that conformed both in size and distribution to the oil deposits seen microscopically.

The case we wish to present has features which are probably due in part to retention of iodized poppyseed oil 40 per cent.

REPORT OF CASE

The patient was a 43 year old white man. He had an original diagnosis of pulmonary tuberculosis in 1927, based on repeated pulmonary hemorrhages and roentgenologic evidence. He underwent multiple hospitalizations, but no collapse therapy was attempted, as roentgenograms showed that the lesions were predominantly fibrotic.

He was first admitted to the Veterans Administration Hospital in San Fernando, Calif., in 1938. In March 1939, at another hospital, an attempt was made to control the multiple small hemorrhages by left pneumothorax, but was unsuccessful. In April it was suspected that a cavity had formed in the right lung, but serial roentgenograms failed to confirm this. The left lung had not changed in roentgenographic appearance for years; it was reported as showing increased hilar density, generalized accentuation of the bronchovascular tree, with hard striations radiating upward above the second rib, and vague calcific deposits in the extreme apex.

An attempt to introduce lipiodol® into the tracheobronchial tree in August 1939 was unsuccessful. Another unsuccessful attempt was made in September. Only an occasional specimen of sputum was positive for acid-fast bacilli, the first being obtained in December 1939. In March 1940 lipiodol® was introduced into the left lung, but the upper lobe was not filled. The iodized oil did fill the lingular and lower lobe branches but gave no clues as to the cause of the repeated pulmonary hemorrhages, which was suspected to lie in the upper lobe.

9. Sheldon, F. B.: Radiology **40**:403, 1943.
10. Brody, H.: Arch. Path. **35**:744, 1943.

Roentgenograms taken subsequently showed some retention of the iodized oil bilaterally until March 1941. On Sept. 24, 1941, 10 cc. of lipiodol[9] was introduced into the left main stem bronchus through a catheter on direct bronchoscopic visualization. Roentgenograms showed iodized oil only in the bronchus to the lower lobe, none being seen in the lingular or other bronchi of the upper lobe. No abnormalities were noted. In April 1942 the roentgenologist reported that no trace of iodized oil remained in the lung.

The patient improved symptomatically and left the hospital. He was readmitted in May 1944, after another pulmonary hemorrhage. While in the hospital he had repeated episodes of hemoptysis. Serial roentgenograms demonstrated little change. Right phrenicotripsy was performed in July 1944 and July 1945, as it was thought that the hemorrhages were coming from that side. Left phrenicotripsy was

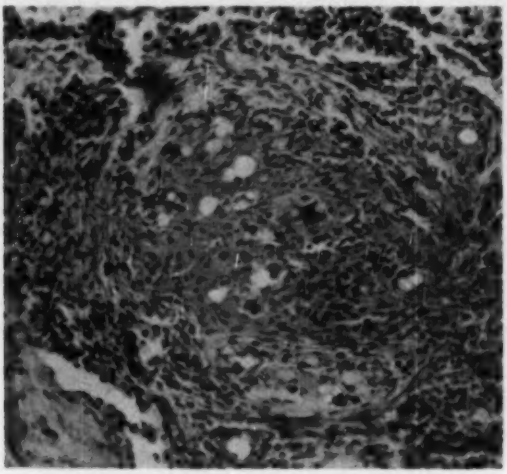

Fig. 1.—Granuloma, foreign body giant cell and scattered oil droplets; hematoxylin and eosin stain.

done in January 1947. None of these measures prevented the repeated small hemorrhages. In May 1947 planigrams revealed a cavity in the left upper parahilar area at 7 and 8 cm. levels. In the following September thoracotomy was done, and in addition to the changes in the upper lobe of the left lung there was considerable infiltration near the hilus in the lower lobe, and it was decided that upper lobe lobectomy would probably not result in a cure; so total left pneumonectomy was done.

The description of the lung was recorded as follows: "The lung weighs 324 Gm. The surfaces of both lobes are characterized by short and long grayish fibrous tags except for a few small smooth areas on the upper lobe. Palpation indicates that both lobes are practically airless; in fact, the margin of the upper lobe feels meaty in consistency. A few marginal blebs are noted along the base. A few scattered minute areas of thickening, 1 to 2 mm. in diameter, are seen and are

palpable in the pleura, presenting the appearance of blocked lymphatic channels with fibrous reaction. Two cavities are found, one in the apex, about 6 mm. in diameter, and the other in the lower mesial region, measuring about 3 by 4 cm. The latter is located adjacent to the bronchus to the upper lobe and connects with it. Part of it, at least, appears to be a widely dilated bronchus. The cavity has a fairly smooth wall except for the bronchial folds. No Rasmussen aneurysm is found. A few small bronchi are connected with the cavity. All of the larger bronchi of the upper lobe show fusiform dilatation with thickened walls, and they extend nearly to the periphery. They contain some yellowish purulent exudate. One small marginal infarct is found near the pleura of the lower lobe. It measures about 1 and 2 cm. in its respective diameters. In the upper lobe one small 5 mm. nodule is suspected of being a tubercle. It is firm and dark gray on section. Several grayish fibrotic foci, 1 mm. or less, are also found near the large cavity and are suspected of being tubercles. The hilar nodes do not measure over 1 cm. in their greatest diameters. They are black, with grayish capsules. The lung

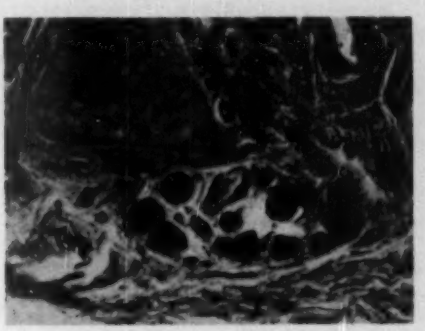

Fig. 2.—Oil droplets revealed in a frozen section by osmic acid stain.

tissue of both lobes is moderately firm, and fibrous tissue is definitely increased along the course of the bronchi. The bronchi of the lower lobe show only minimal cylindric dilatation."

It was noted in routine paraffin sections that there were foci of granulomatous tissue with occasional foreign body giant cells surrounding circular spaces (fig. 1). Mononuclear phagocytes also contained circular spaces. An oil granuloma was suspected, and further studies were made.

The apical cavity appeared to be a group of dilated alveoli with a few foci of round cells and a partial lining of cuboidal epithelium.

The large cavity showed a zone of chronic inflammatory cells with some eosinophilic granulocytes. Small areas of epithelial regeneration were seen, but there were no definite lesions which could be considered of tuberculous origin. Sections through the fibrotic foci near the large cavity revealed typical healing tubercles, some with early calcific changes. The dilated bronchi of the upper lobe revealed typical microscopic features of cylindric bronchiectasis. Sections through the infarct were typical, but no cause was evident. Lymph nodes revealed no oil droplets.

Sections taken in the vicinity of the bronchi to the lower lobe revealed spaces surrounded by fibroblasts, small amounts of collagen and collections of lymphocytes with an eosinophilic cell here and there. These areas did not contain typical epithelioid cells and showed features differing from those of tubercles and tuberculous granulation tissue. There were collections of phagocytic cells containing brown pigment and either oil or vacuoles. Sudan stain and osmic acid stain (fig. 2) revealed oil droplets. The largest droplets appeared to be either in lymphatic vessels or surrounded by tissue reaction elements. In some sections alveoli contained many red blood cells. A similar condition has been noted where fuel oil was aspirated, and was believed to be a toxic response.[11]

Starch tests on thin slices of lung tissue were negative, indicating that there was no dissociation of the iodized oil. Examination of thin slabs of tissue failed to show iodized oil, probably because of the small size of oil droplet foci. On being questioned, the patient stated that he seldom, if ever, used nose drops, which helps to exclude liquid petrolatum as the offending agent. Also, according to Black,[12] liquid petrolatum does not stain with osmic acid.

While many of the macrophages contain fat, as evidenced by fat stains, many of the "fat droplets" are probably vacuoles, as they do not stain with either sudan or osmic acid.

According to the work of Goddard,[13] we may be dealing with an anaphylactic picture, especially since some of our sections show small areas which may be similar to the myxomatoid degeneration he described.

While our case does not present so striking a picture as that of Brody,[10] we are of the opinion that more instances of granuloma due to retained iodized poppyseed oil would be recognized if this condition were kept in mind, especially in cases in which iodized oil bronchography is practiced.

SUMMARY

A patient with a diagnosis of pulmonary tuberculosis and bronchiectasis, with repeated hemorrhages, was afforded complete symptomatic relief by pneumonectomy. Pathologic examination of the removed lung revealed granulomatous lesions (iodized poppyseed oil granuloma) which were presumed to be due to previous instillations of lipiodol.®

11. Kurtz, J. E.: Arch. Path. **48**:259, 1948.
12. Black, C. E.: J. Lab. & Clin. Med. **23**:1027, 1938.
13. Goddard, J. W.: Am. J. Path. **23**:943, 1947.

VASCULAR LESIONS IN LIPID PNEUMONIA (DUE TO LIQUID PETROLATUM)

Pathogenesis and Significance

EDWARD V. HASTINGS, M.D.*
MILWAUKEE

REACTIONS of the body in general, and of the lungs in particular, to animal and vegetable oils and petroleum derivatives have intrigued investigators for almost three decades. The vast amount of work accomplished in this field was originally stimulated by the experimental studies of Guieysse-Pellissier [1] in 1920 and Corper and Freed [2] in 1922. However, it was not until 1925 that the reaction produced by one of these substances in the human lung was recorded. In that year an instance of lipid pneumonia (lipoid pneumonia, oil aspiration pneumonia) of the infantile type was presented by Laughlen.[3] With attention thus focused, recognition of the disease became widespread and reports thereof numerous. In 1941 Kaplan [4] was able to collect 411 cases. In general, the contributors reporting these cases attempted to add to the known facts concerning the following aspects of the problem: (1) the specific cause and effect as evidenced in the experimental animal, (2) precautions to be taken and complications to be anticipated in the clinical use of the various types of oils, (3) clinical and roentgen diagnosis of the disease, (4) ability of the disease to simulate bronchogenic carcinoma and (5) the pathologic anatomy of the lesion. The purpose of this report, presenting 2 additional cases, is twofold: first, to review the vascular lesions which may sometimes occur and trace their pathogenesis; second, to point out that instrumentation of the tracheobronchial tree may be extremely hazardous in cases so involved.

REPORT OF CASES

CASE 1.—A 42 year old white woman was admitted to Oliver General Hospital, Feb. 9, 1949, for evaluation of a pulmonary abnormality discovered during a mass roentgenographic survey several months previously. She stated that she had felt well until approximately two years before, when she began to experience pain in

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From the Laboratory Service, Oliver General Hospital, Augusta, Ga.

1. Guieysse-Pellissier: Compt. rend. Soc. de biol. **83**:809, 1920.
2. Corper, H. J., and Freed, H.: J. A. M. A. **79**:1739, 1922.
3. Laughlen, G. F.: Am. J. Path. **1**:407, 1925.
4. Kaplan, I.: Am. J. Dis. Child. **62**:1217, 1941.

the right half of the chest laterally; this was sharp, intermittent, and did not radiate. It was not incapacitating but had become more frequent during the past one to two months.

The patient had suffered an injury at birth, with facial paralysis, neurologic changes in the left arm and leg, a permanent defect of speech and some difficulty in deglutition.

Physical examination revealed nothing of significance except for the speech defect and small nodules in the breasts. The clinical diagnosis in the latter regard was cystic hyperplasia, mild.

Laboratory studies gave the following results: white blood cell count and hemoglobin level, normal; corrected sedimentation rate, 30 mm. per hour; vital

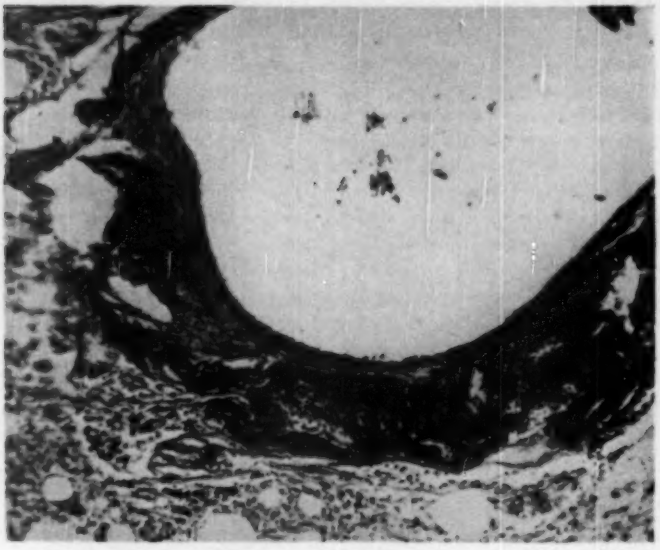

Fig. 1.—Elastic tissue has replaced all but a small segment of muscularis at the left; Verhoeff stain; × 110.

capacity, 60 per cent below normal for height and weight; basal metabolic rate, minus 29; serologic tests of the blood, negative; sputum, negative for acid-fast bacilli on direct smear (no additional sputum studies requested).

Roentgenograms of the abdomen and the dorsal and lumbar spine revealed no abnormalities. Stereoscopic examination of the chest disclosed in the right middle lung field a somewhat mottled density, which appeared to be located anteriorly. It was felt by the examiner that this density would conform to the shape of an atelectatic middle lobe of the right lung.

During her course in the hospital the patient was entirely afebrile and asymptomatic except for mild nonproductive cough. Because of the radiographic changes in the right lung, the cough and the easy fatigability of the patient noted by

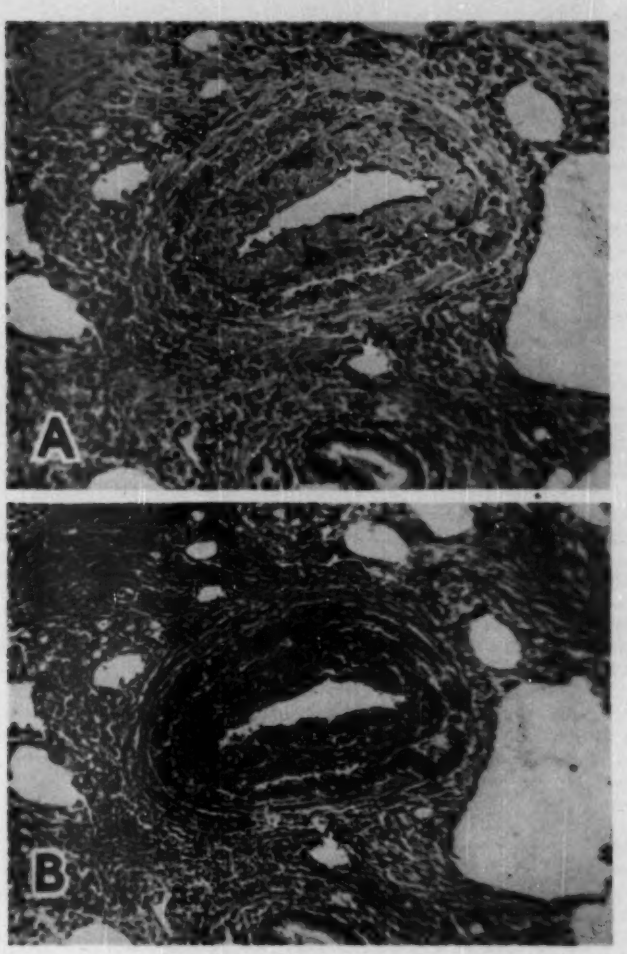

Fig. 2.—(*a*) Thickened arteriole consisting of hyperplastic elastic tissue and degenerating muscularis; hematoxylin-eosin stain; × 135. (*b*) Same section restained by Vorhoeff's technic; × 135.

relatives, it was decided that bronchoscopy was indicated to determine the cause of the pulmonary atelectasis. The instrument was readily introduced into the trachea with the patient under general anesthesia and was passed to the level of the right middle lobe bronchus. During the procedure, inspection revealed no abnormalities, and the ostium of the questionable bronchus was normal to the line of possible vision. Nevertheless, it was decided to make a biopsy of this zone to rule out any underlying pathologic process. A forceps was then introduced, but removal of a specimen was found to be impossible with this instrument because of a defective part at the handle. Consequently, the forceps was withdrawn, and immediately thereafter inspection revealed a large amount of blood within the right bronchial tree. Vision was completely obscured, and the bronchoscope was withdrawn. Profuse bleeding ensued, with exsanguination and death resulting within a few minutes.

Questioning of the patient's mother revealed that the patient had been a habitual user of "oily" nose drops for many years. The exact type of oil was not known. However, it was stated that this material had not been used for the past one and one-half to two years.

Necropsy (approximately one hour after death).—The significant gross findings were confined to the chest. The pleural cavities contained no free fluid, and there were no adhesions. The right lung weighed 325 Gm. The pleura of the upper and lower lobes was smooth except for small areas of grayish white scarring. Such areas measured up to 0.5 cm. in diameter and on section were seen to overlie superficial grayish white or grayish yellow zones of indurated parenchyma. The middle lobe was contracted, hard and airless. The irregularly nodular surface was covered by smooth pleura. Sections in the long axis of the lobe revealed solid, distinctly yellow substance at the periphery; near the hilus the consolidated tissue was mottled grayish yellow and grayish black. Oily material could be obtained by scraping the cut surface. The bronchial tree was completely filled with blood. Careful dissection and search disclosed no interruption of the continuity of the mucosa. The left lung weighed 250 Gm. Search was of no avail concerning a bleeding point. In the midportion of the upper lobe anteriorly there was a hard nodule, 3.5 cm. in diameter, which presented gross features essentially the same as those seen in the middle lobe of the right lung.

Microscopic examination revealed a typical picture of lipid pneumonia of the adult type (paraffinoma). The material responsible for the lesion was identified as a petrolatum derivative, probably liquid petrolatum. Stained with sudan IV this material was orange to orange-yellow; with nile blue sulfate, faint pink; to osmic acid it was negative. Pulmonary vascular disease formed the most interesting part of the histologic study. The earliest morphologic evidence of involvement consisted of thickening (edema) of the intima, which was infiltrated by lymphocytes and plasma cells. This was followed by alteration of the muscular layer, in which there was gradual disappearance of nuclei. At this stage such zones exhibited a homogeneous staining reaction in hematoxylin and eosin preparations. This was demonstrated to be due to the fact that proliferating elastic tissue had replaced the muscularis (fig. 1). The subsequent course of the lesion consisted of progressive increase of elastic fibers with terminal contraction and decrease of vascular caliber (figs. 2 and 3). The end result was a solid elastic tissue scar. These changes involved vessels of all sizes. Figure 4 illustrates a bronchus surrounded by cartilage and vessels exhibiting partial involvement. Ulceration was not uncommon in the smaller branches of the bronchi. In the densely hyalinized foci, occasional vessels were seen containing lipid deposits within their lumens.

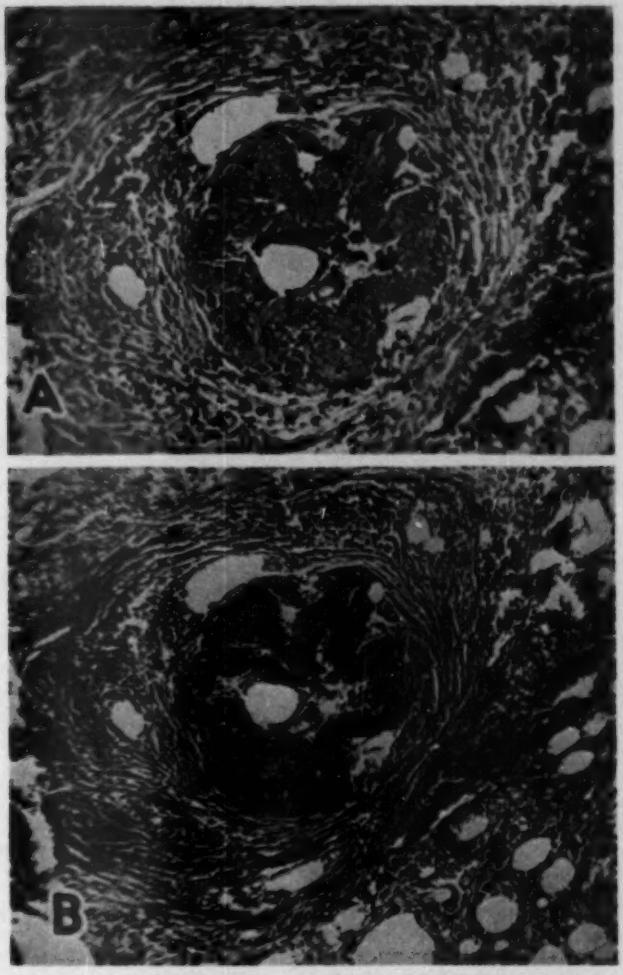

Fig. 3.—(*a*) An obliterated lumen lies just to the right of the large central vacuole, which is surrounded on one side by the compressed nuclei of the phagocyte it occupies; × 135. (*b*) Same section stained by Verhoeff's technic.

CASE 2.—A 66 year old white man was admitted to the University of Georgia Hospital, March 27, 1948, because of cough and wheezing respiration of many years' duration. Dyspnea on exertion was slowly increasing. In October 1947 these symptoms became worse, with paroxysmal cough, which was productive of a moderate amount of mucoid sputum. There was no history of hemoptysis. There was slight bilateral pain in the chest, which the patient attributed to coughing.

Physical examination revealed an emphysematous chest. The trachea was in the midline. Breath sounds were diminished on the right, especially over the middle and lower lobes of the lung.

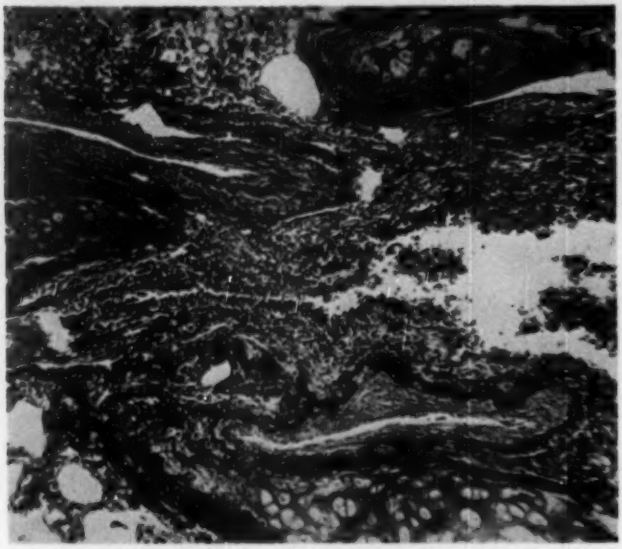

Fig. 4.—A bronchus with associated vessels which exhibit beginning elastic tissue replacement of the muscular layer; Verhoeff stain; × 110.

Roentgen examination revealed atelectasis of a considerable portion of the lower lobe of the right lung, with regression of the mediastinal border and a suggestion of atelectasis or infiltration in the middle lobe.

On March 29 the patient was given bronchoscopic examination. There was generalized reddening of the bronchial mucosa. The lower lobe bronchi were stenotic, the obstruction seeming to be cicatricial rather than neoplastic. Biopsy of this area revealed cartilage. An effort to remove granulation tissue below the point of narrowing resulted in profuse hemorrhage. The bleeding stopped, but circulatory collapse had occurred and the patient died shortly thereafter.

After the patient's death it was learned from relatives that he had been a habitual user of liquid petrolatum, instilling it into his nostrils by atomizer. In recent years he had daily sniffed "mentholated oil and vaseline®" into his nostrils.

Necropsy (Dr. Fred Dick Jr.).—Filmy fibrous tissue bound the visceral to the parietal pleura on each side. Posteriorly the lower lobe of the left lung presented a firm, irregular, yellowish white mass (5 by 3 by 3 cm.) which was adherent to the seventh rib in the midscapular line. Sections of this lesion revealed a central zone of yellowish white amorphous material surrounded by a zone of dense fibrous tissue. A similar mass (5 by 5 by 4 cm.) occupied most of the middle lobe of the right lung, extending to the hilus and across the fissure into the lower lobe. Within this mass were small cystic spaces, measuring up to 0.5 cm. in diameter, which were filled with clear yellow oily material. The tracheobronchial tree contained clotted and fluid blood. However, the source of the bleeding could not be determined. In fact, the exact site at which tissue was taken for biopsy could not be accurately located.

Microscopically, the areas of fibrosis and cavitation contained lipid material in small and large droplets associated with foreign body giant cells. This substance stained pink with sudan IV and did not reduce osmic acid. Vascular lesions were less frequently seen than in case 1. The early stage of involvement was more conspicuous.

COMMENT

The present study was stimulated by the sudden deaths of 2 patients at different hospitals under strikingly similar circumstances. Each patient had lipid pneumonia of the adult type, and each died of severe pulmonary hemorrhage during bronchoscopic examination. As a result, tissue obtained at necropsy in each case was carefully studied to determine the presence of any form of vascular disease.

The fact that vascular involvement occasionally occurs in lipid pneumonia due to liquid petrolatum had been pointed out previously by Graef [5] and Pinkerton.[6] The former found vascular lesions in 1 of the 15 cases he reported in 1939. The latter, in 1940, reported a case in which the liver and the spleen contained tubercle-like lesions which consisted of masses of liquid petrolatum; the pulmonary vessels "contained globules of liquid petrolatum surrounded by fibrous tissue to resemble normal adipose tissue." It was felt by this author that the vascular lesions may have been the starting point for the oil emboli. A similar vascular lesion was seen in one of the cases observed at this hospital, and the spleen contained microscopic lipid deposits.

The widespread necrotizing arteritis and periarteritis reported by Young, and associates [7] to occur with oil of animal origin differs considerably from the vascular disease due to liquid petrolatum. This difference is probably related to the free fatty acid content and the rapidity of hydrolysis. These factors are very low in liquid petrolatum and high in animal oil, such as cod liver oil.

5. Graef, I.: Arch. Path. **28**:613, 1939.

6. Pinkerton, H., and Moragues, V.: Arch. Path. **29**:691, 1940.

7. Young, A. M.; Applebaum, H. S., and Wassermann, P. B.: J. A. M. A. **112**:2406, 1939.

The evidence obtained during this study indicates that in pneumonia due to liquid petrolatum the vessel changes occur in three stages. The initial alteration consists of intimal swelling due to edema with lymphocytic and plasma cell infiltration. The duration of this stage is unknown. Degeneration of the muscular elements follows with gradual loss of cellular and nuclear detail. The damaged muscle layer is then replaced by proliferation of elastic tissue. Hematoxylin and eosin preparations reveal at the completion of this substitution process a thickened wall which is faintly basophilic, homogeneous and acellular. The third stage consists of continuing proliferation of elastic tissue with progressive contraction and narrowing of the lumen. The end result is a circumscribed solid scar of elastic tissue.

No difficulty has been encountered in distinguishing these changes from those which are commonly labeled "atrophy of disuse."

In view of the terminal pulmonary hemorrhage in these cases it was felt that an attempt to correlate the prolonged bleeding with the vascular changes was indicated. It was not possible, however, to demonstrate the exact site of the bleeding. Nonetheless, the evidence at hand seems to justify the suspicion that blood vessel disease played a role in the demise of each of these patients. Two possible ways are suggested in which this might occur: 1. Bronchial biopsy might disrupt the continuity of a vessel which had been altered to such an extent that the intrinsic factors concerned with hemostasis were lacking or functionally inactive. 2. It has been demonstrated that the superficial bronchial vessels were not spared (fig. 4). Conceivably, such a vessel could be exposed by trauma incident to instrumentation without biopsy.

SUMMARY

Two cases of lipid pneumonia, adult type, due to liquid petrolatum are presented. Severe pulmonary hemorrhage was the immediate cause of death in each case. This followed bronchoscopy alone in one instance and bronchoscopy with biopsy in the other. The vascular lesions occurring in this disease are described in detail. The possible clinical significance of these changes in regard to instrumentation is indicated.

Drs. Edgar R. Pund and Robert C. Major gave me permission to use case 2.

Milwaukee County Hospital.

ANEMIC INFARCT OF THE LIVER

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DISTURBANCES of the arterial blood supply of the liver have been studied throughout the years. Experimental sudden occlusion of the intact hepatic artery results in death, due to anoxemia and massive infarction of the liver.[1] On the other hand, the animals survive if the ligation of the arteries supplying the liver is performed in multiple stages, thus proving that the vital functions can be maintained if the time is sufficient to allow a gradual readjustment of the circulation.[2]

In man the effects of accidental or intentional ligation of the hepatic artery or of one of its main branches are essentially the same as those experimentally produced—resulting in infarcts or massive necrosis of the liver.[3] The cases include ligation of the hepatic artery or its branches during the course of some operative procedure, such as cholecystectomy, gastric resections or therapeutic ligation of the hepatic artery for aneurysms.[4] In some of these cases the slow obstruction of aneurysmatic blood vessels and in others the possible presence of anomalous or accessory arteries may have accounted for the establishment of sufficient collateral circulation to prevent extensive damage of the liver.[5]

Pass [6] collected 52 cases of true anemic infarction of the liver that fulfil the essential requirements of spontaneous anemic infarcts, not

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1. Whipple, G. H., and Sperry, J. A.: Bull. Johns Hopkins Hosp. **20**:278, 1909. Behrend, M.: Surg., Gynec. & Obst. **31**:182, 1920. Cameron, H. C., and Mayes, B. T.: J. Path. & Bact. **33**:799, 1930.

2. Huggins, C., and Post, J.: Arch. Surg. **35**:878, 1937.

3. (*a*) Gerlach, W., in Henke, F., and Lubarsch, O.: Handbuch der speziellen Pathologie und Histologie, Berlin, Julius Springer, 1930, pt. 1, p. 71. (*b*) Graham, R. R., and Cannell, D.: Brit. J. Surg. **20**:566, 1932-1933. (*c*) Kerr, R. W.: J. Kansas M. Soc. **34**:175, 1933.

4. Smith, R. E.: Brit. J. Surg. **8**:532, 1920-1921. von Hofmeister, F.: Zentralbl. f. Chir. **49**:154, 1922.

5. Merkel, H.: Virchows Arch. f. path. Anat. **214**:289, 1913. Segall, H. N.: Surg., Gynec. & Obst. **37**:157, 1923.

6. Pass, I. J.: Am. J. Path. **10**:66, 1935.

counting cases of hepatic necrosis due to trauma or surgical intervention. In 22 of the cases the infarct was caused by periarteritis nodosa; in the remaining cases it was the result of embolism or thrombosis, "end-arteritis" and hypoplasia of the hepatic arteries. Seventeen additional cases have been reported in the past fourteen years by various authors.[7] They include similar etiologic factors, as well as metastatic carcinoma of the liver producing compression and thrombosis of branches of the hepatic artery in 2 cases.

The possible etiologic factors recorded in the literature are summarized in the table. Because of its rare occurrence we consider true anemic infarction of the liver of sufficient interest to report a case which we encountered in our autopsy material.

REPORT OF A CASE

A 60 year old white man was admitted to the hospital with symptoms of left hemiplegia, which followed a cerebral vascular accident three years earlier. The

Cases of Infarction of the Liver Recorded in the Literature

Mechanism of Infarction	Secondary to	Cases
Periarteritis nodosa		20
Embolism of hepatic artery	Mural thrombi of the heart	8
Embolism of hepatic artery	Paradoxic embolism	2
Embolism of hepatic artery	Subacute bacterial endocarditis	18
Thrombosis of the hepatic artery	Thrombus in aneurysm of hepatic artery	5
Thrombosis of the hepatic artery	Infection of the biliary tract	2
Thrombosis of the hepatic artery	Metastatic carcinoma of liver	2
Thrombosis of the hepatic artery	Compression of main hepatic artery by extension of carcinoma of the stomach	1
Thrombosis of the hepatic artery	Mycotic aneurysm of hepatic artery	1
Endarteritis of the hepatic artery		2
Hypoplasia of the hepatic artery		1
Undetermined cause		2
	Total	70

patient had been known to have vascular hypertension for many years. Eight years before admission he underwent a "gallbladder operation," supposedly cholecystostomy.

Physical examination revealed a bedridden patient who presented the picture of left hemiplegia, with marked contracture of the left arm. His blood pressure reading was 180 mm. of mercury systolic and 90 mm. diastolic. The heart appeared normal. The laboratory findings were essentially negative.

Three months after admission the patient was suddenly seized with severe precordial and interscapular pain. The blood pressure dropped to 118 systolic and 70 diastolic. The clinical impression was that of coronary thrombosis, later confirmed by electrocardiographic examination, which showed evidence of infarction of the posterior wall. The patient recovered, and a normal electrocardiogram was obtained, within the following six weeks.

7. (*a*) Seligman, B.: Am. J. M. Sc. **179**:609, 1930. (*b*) Lund, H.: Stewart, H. L., and Lieber, M.: Am. J. Path. **11**:157, 1935. (*c*) Spiegel, R.: Arch. Int. Med. **58**:993, 1936. (*d*) Schlesinger, E. R.: J. Mt. Sinai Hosp. **4**:122, 1937. (*e*) Case Records, Massachusetts General Hospital, New England J. Med. **231**: 850, 1944; **235**:441 and 521, 1946.

Three months after this incident, the patient suddenly experienced excruciating pains in the right arm, the midback and the left leg. He was frankly cyanotic, and all four extremities had a marble-like livid appearance. There was a slight icteric tinge of skin and scleras. The blood pressure was 140 systolic and 75 diastolic. The entire abdomen was slightly rigid, and the temperature rose to 106.4 F. after four hours. The blood count showed 12,000 polymorphonuclear leukocytes. The sedimentation rate was 55 (Westergren), and the urinalysis revealed the presence of bilirubin and urobilinogen.

After sixteen hours the temperature dropped to normal; however, the pains in the extremities and the midback increased in severity, followed by vomiting. Abdominal pain set in, which increased rapidly in intensity and was localized in the right upper quadrant. The icterus became more intense. The urine still contained bile and urobilinogen, and the sediment showed occasional polymorphonuclear

Fig. 1.—Infarct of the right lobe of the liver.

leukocytes, erythrocytes and hyaline and granular casts. At this time surgical intervention was contemplated, but was rejected because of the patient's poor condition. The circulation began to fail and the patient died ninety-six hours after the onset of this last episode.

Postmortem Observations.—Postmortem examination revealed extensive myofibrosis of the posterior wall of the left ventricle of the heart, which weighed 500 Gm. The annulus fibrosus of the mitral valve was notably calcified. The endocardium of the left ventricle was considerably thickened. In the left auricular appendage there was a small mural thrombus. The coronary arteries revealed extensive sclerosis and calcification with marked narrowing of the lumen. There was no gross evidence of recent infarction. The lungs were congested and edematous, and in the lower lobe of the left lung there were focal areas of consolidation.

The liver weighed 1,440 Gm. The capsule was smooth and glistening. The consistency was firm. On sectioning, the picture was that of acute congestion. In the posterior superior aspect of the right lobe there was a wedge-shaped infarct extending under the capsule and measuring 8 cm. in length and 6 cm. in its longest transverse diameter (fig. 1). It was well demarcated, firm, elevated over the surface and appeared dark red mottled with yellow-brown areas. The larger branches of the right hepatic artery were patent. However, in the vicinity of the lesion some of its small branches contained emboli. Many of the small and large branches of the portal vein were occluded by adherent thrombi.

The gallbladder was small, contracted, and adhered to the transverse colon with dense fibrous tissue. The lumen contained about 10 cc. of yellow-brown, tenacious bile. The wall was edematous, thickened and fibrotic. The mucosa was scarred and in places showed shallow ulcers, which were covered with a thin yellow-gray fibrinous exudate. The extrahepatic bile ducts were patent. The kidneys showed the typical picture of arteriolosclerotic nephrosclerosis. The mesenteric blood vessels were patent throughout. The remaining abdominal organs showed no changes. Permission for examination of the brain was not obtained.

Microscopic Observations.—Liver: The infarcted area revealed extensive coagulation necrosis of the hepatic parenchyma, with but small islands of more or less intact tissue left. The liver cells appeared as homogeneous eosinophilic fragments, frequently with indistinct cellular outlines. Some of them contained shrunken, pyknotic nuclei, while others were free from nuclear contents. Reticulum stain revealed the argentophil fibers to be preserved and intact. The periphery of the infarcted area was extensively infiltrated with polymorphonuclear leukocytes and a few lymphocytes, which in places were seen to invade the necrotic tissue (fig. 2*A*). Occasionally small biliary infarcts were noted. The smaller radicles of the hepatic artery frequently revealed proliferation of the intima, which produced marked narrowing of the lumen. Van Gieson elastica stains showed the internal elastic lamina to be preserved, though occasionally it was split or duplicated. The muscular layer and the adventitia were of normal thickness and showed no changes. Several of the arteries were occluded by organized emboli, which were pierced by small, newly formed capillaries lined by endothelial cells. Other small branches of the hepatic artery were plugged by more recent emboli, which had been invaded by occasional fibroblasts (fig. 2*B*). The larger and smaller branches of the portal vein were occluded by thrombi, which extended frequently into the interlobular veins. All layers of the involved vessels, particularly the intima, were infiltrated by polymorphonuclear leukocytes and round cells, which here and there were seen to penetrate into the surrounding parenchyma. The remaining liver tissue showed the picture of passive congestion and moderate fatty metamorphosis of the liver cells surrounding the centrolobular areas.

Gallbladder: The gallbladder showed marked fibrosis of all layers, particularly of the subserosa and the mucosa. The latter was diffusely infiltrated with polymorphonuclear leukocytes and occasionally revealed small, shallow ulcers covered with fibrinous exudate.

Heart: Sections from the posterior wall of the left ventricle revealed extensive replacement fibrosis. The muscle fibers were increased in diameter. The cross striation was preserved. The left auricular appendage contained a mural thrombus. The coronary arteries revealed extensive thickening and sclerosis of the intima, which frequently contained massive calcium deposits.

Other Organs: The microscopic examination of the remaining organs confirmed the gross findings.

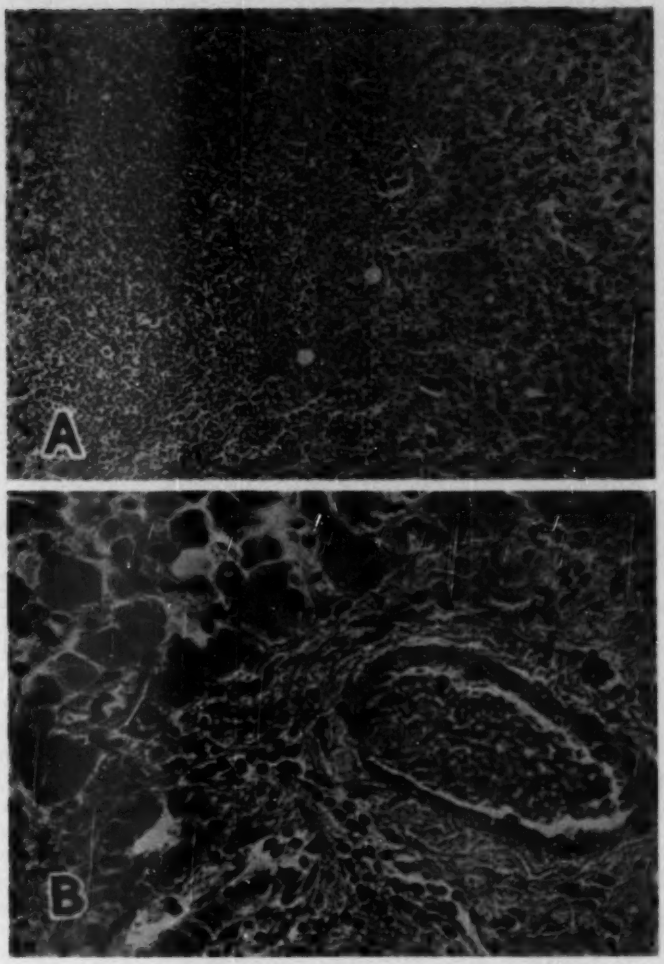

Fig. 2.—*A*, border of the infarct showing active leukocytic infiltration at the line of demarcation; hematoxylin-eosin; × 140. *B*, embolus in a branch of the right hepatic artery; hematoxylin-eosin; × 320.

Histologic Diagnoses.—Anemic infarct of the right hepatic lobe; recent embolism of the small branches of the right hepatic artery; organized emboli in several of the small branches of the right hepatic artery; pylephlebitis; chronic recurrent cholecystitis; chronic pericholecystitis; myofibrosis cordis, extensive; prominent arteriosclerosis of the coronary arteries; arteriolosclerotic nephrosclerosis; extensive arteriosclerosis, involving the splenic, hepatic, pancreatic and pulmonary arteries; focal bronchopneumonia of the lower lobe of the left lung; pulmonary edema and congestion.

COMMENT

The history of this patient suggests three major vascular incidents, the first in the brain, the second in the heart and the third in the liver. The most interesting abnormalities observed at autopsy were those in the liver. There were marked sclerotic changes in the smaller branches of the right hepatic artery, with considerable narrowing of the lumen.

Sclerosis of the hepatic vessels is comparatively rare,[8] and, if present, it is usually without consequence, mainly because the dual vascular supply assures adequate nutrition of the hepatic parenchyma.

While there is agreement in general as to the portal blood supply of the hepatic lobule, the exact nature of the form of communication between the branches of the portal vein and the hepatic artery is still a matter of controversy and study. Following the early work of Kiernan,[9] which demonstrated that the terminal branches of the hepatic artery supply the structures of the portal fields, it was assumed for a long time that these capillaries eventually form venules which at last terminate in the hepatic sinusoids, thus establishing an arteriovenous communication within the portal fields. It was shown in later years, however, that the communication of portal vein and hepatic artery takes place actually within the hepatic lobule and that the venules posited do not exist.[10]

Experiments with visualizing material[11] have shown that blood from the radicles of both the hepatic artery and the portal vein enters the sinusoids of the hepatic lobule at its periphery, where the mixing of the arterial and venous blood takes place. This connection is accomplished by an arteriole which, after traversing the septum, divides into capillaries that supply the adjacent sinusoids. The junctions of the arterial capillaries, according to Olds and Stafford,[12] are always inde-

8. Wartman, W. B.: Am. J. M. Sc. **186**:27, 1933. Papp, C.: Virchows Arch. f. path. Anat. **290**:551, 1933.

9. Kiernan, F.: Phil, Tr., London **123**:711, 1833.

10. Mall, F. P.: Am. J. Anat. **5**:227, 1906. Fissinger, N., and Walter, H.: L'exploration functionelle du foie et l'insuffisance hépatique, Paris, Masson & Cie, 1925. Aunap, E.: Ztschr. f. mikr. -anat. Forsch. **25**:238, 1931.

11. Gilbert, A., and Villaret, M.: Compt. rend. Soc. de biol. **67**:521, 1909.

12. Olds, J. M., and Stafford, E. S.: Bull. Johns Hopkins Hosp. **47**:176, 1930.

pendent of, and at some distance from, the similar communications established by the veins. In a more recent study [13] it was found that although some of the arterial terminals emptied directly into the sinusoids of the lobules, some communicated with the portal radicles before the latter reached the sinusoids and that there were also arteriovenous anastomoses between the branches of the artery and the portal vein as they passed through the interlobular spaces.

The dual blood supply no doubt prevents hepatic necrosis in occlusion of the portal circulation. It also accounts for the fact that there is rarely hepatic necrosis unless massive occlusion of the hepatic artery is present. There possibly are other factors accounting for the rarity of spontaneous infarction of the liver. The anatomic arrangement of the hepatic artery renders embolization very difficult.[6] Collateral blood supply probably plays an important part in the prevention of infarction of the liver.[14] Furthermore, the liver cells are highly resistant to anemia, as shown experimentally,[15] and in some cases the hepatic infarcts may not be recognized, because they have been transformed into abscesses.[16]

Occlusion of the portal vein or of its branches does not cause necrosis of the liver in the presence of an adequate arterial blood supply. The frequent accidental finding of completely thrombosed portal veins without necrosis of the hepatic parenchyma has repeatedly been reported. Moreover, experimental ligation of the portal vein of animals is usually uneventful as far as infarction of the liver is concerned. The simple "red infarcts" or "atrophic red infarcts" described by Zahn [16] follow occlusion of the portal vein only when there is impairment of the arterial circulation, as seen in heart failure. Here one finds dilatation of the sinuses and atrophy of the liver cords, while necrosis of the liver cells is absent.

Since in the presented case the emboli in several of the small branches of the right hepatic artery showed beginning organization we believe that this embolization was the older lesion, whereas the portal thrombosis, possibly secondary to a flare-up of the lesion in the gallbladder, was of recent date. The arterial blood supply was further decreased by an active sclerosing process that had occurred previously in the small branches of the hepatic artery. When the pylephlebitis occurred, the total blood supply of the liver tissue of the area supplied by the recently occluded arteries became altogether insufficient, with ischemia and necrosis of the hepatic parenchyma resulting. The organized emboli found in some of the other branches of the hepatic artery were old. The development of a corollary circulation and recanalization of the

13. Wakim, K. G., and Mann, F. C.: Anat. Rec. **82**:233, 1942.
14. Zimmerman, H. M.: Arch. Path. **10**:66, 1930.
15. Chandler, L. R.: Proc. Soc. Exper. Biol. & Med. **18**:23, 1920-1921.
16. Zahn, F. W.: Verhandl. d. Deutsch. Naturf. u. Aerzte **2**:9, 1898.

clots probably prevented necrosis of the hepatic tissue at the time when embolization of those vessels occurred.

In reviewing the previous reports on embolization of the hepatic artery secondary to the presence of mural thrombi of the heart we encountered a total of 7 cases.[17] Of these, only 1 of 2 cases reported by Schlesinger[7d] resembled the presented case. That case was similar to ours in that there was acute inflammatory involvement of the biliary tract associated with embolic occlusion of the main branch of the left hepatic artery, which was secondary to the dislodging of a mural thrombus from the left auricle. In that case, however, there was no thrombosis of the portal vein.

Our case seems to be of interest because it shows hepatic necrosis due to portal occlusion in an area where the arterial blood supply had been previously disturbed.

SUMMARY

A case is reported in which a true anemic infarct of the liver secondary to thrombosis of branches of the portal vein was superimposed on arteriosclerotic changes and embolism of the right hepatic artery secondary to the presence of a mural thrombus of the left auricular appendage. It is assumed that the portal thrombosis developed secondary to a flare-up of chronic cholecystitis and precipitated the necrosis in an area the blood supply of which had previously been altered because of old and more recent embolic occlusion of branches of the hepatic artery.

17. (*a*) Baldwin, F. A.: J. M. Research **8**:431, 1902. (*b*) Wiessner, J. M. P.: Ein Fall von anämischen Leberinfarkten, Inaug. Dissert., Erlangen, Junge & Sohn, 1917. (*c*) Askanazy, M.: Rev. méd. de la Suisse Rom. **38**:653, 1918. (*d*) Mittasch, G.: Virchows Arch. f. path. Anat. **251**:638, 1924; cited by Pass.[6] (*e*) Seligman.[7a] (*f*) Schlesinger.[7d]

INCIDENCE OF GANGRENE OF THE EXTREMITIES IN NONDIABETIC AND IN DIABETIC PERSONS

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MINNEAPOLIS

IT IS a common observation that elderly diabetic subjects are more prone to the development of gangrene of the lower extremities than nondiabetic persons of corresponding age. This study was undertaken to determine quantitatively the importance of diabetes in the development of gangrene. An analysis was made of all the postmortem records filed in the department of pathology of the University of Minnesota from 1910 through 1947. Since the records reveal no cases of gangrene of the extremities of children who were in the first decade of life, all subjects under 10 years of age have been omitted from consideration in the tables. The postmortem records analyzed represent 28,240 males and 15,119 females over 10 years of age.

INCIDENCE ACCORDING TO AGE, SEX, EXTREMITY INVOLVED AND PRIMARY DISEASE

In tables 1 and 2 all the cases of gangrene of the extremities are listed by decades of life. There were 302 cases involving males and 217 involving females. Of the 519 instances of gangrene, 504 involved the lower and only 15 the upper extremities. In 4 of the 15 cases of gangrene of an upper extremity the condition was due to trauma and fracture; 3, to frostbite; in 1, to thrombosis, and in 4, to embolism. In 3 cases it was caused by arteriosclerosis, and in 1 of these the patient was diabetic.

Trauma.—There were 11 instances of gangrene due to trauma associated with fracture. Eight of the patients were males, and 3 were females. In 4 patients the gangrene involved an arm and in 7 a leg.

Frostbite.—There were 13 examples of gangrene due to frostbite; 12 of the patients were males and 1 a female. In 3 of these an upper extremity was involved.

Acute Arteritis.—Acute arteritis is defined as thromboarteritis not associated with atherosclerosis. There were 21 examples of gangrene due to acute arteritis. Eleven of the patients were males, and 10 were females. In 1 patient the gangrene involved an arm. Ten of the

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patients were under 40 years of age, and it is fairly certain that they did not have atherosclerosis. In the older patients atherosclerosis may have been a contributory factor, but the arteries were occluded by fresh thrombi.

Embolism.—Embolism is an important cause of gangrene of an extremity, and there were 63 examples of this lesion. Nearly all the patients had heart disease of some form with mural thrombi in the

TABLE 1.—*Incidence of Gangrene of the Extremities in Males*

Decade	Autopsies	Trauma	Frost-bite	Acute Arteritis	Embolism	Non-diabetic Athero-sclerosis	Diabetic Athero-sclerosis
10-20	941	0	0	0	0	0	0
20-30	1,820	2	1	1	0	0	1
30-40	2,802	1	1	4	1	0	0
40-50	4,489	2	4	0	2	3	5
50-60	5,940	2	1	2	6	12	20
60-70	6,971	1	3	2	12	27	45
70-80	5,231	0	2	2	6	28	40
80-93	1,818	0	0	0	3	41	8
Total	28,240	8	12	11	30	119	122

TABLE 2.—*Incidence of Gangrene of the Extremities in Females*

Decade	Autopsies	Trauma	Frost-bite	Acute Arteritis	Embolism	Non-diabetic Athero-sclerosis	Diabetic Athero-sclerosis
10-20	811	1	0	0	0	0	0
20-30	1,612	0	0	2	1	0	0
30-40	1,879	0	0	3	4	0	0
40-50	2,209	0	0	1	3	0	3
50-60	2,603	1	1	1	7	7	23
60-70	2,726	0	0	2	6	17	55
70-80	2,534	1	0	1	11	19	35
80-100	947	0	0	0	1	5	6
Total	15,119	3	1	10	33	48	122

left atrium or in the left ventricle. Coronary disease with mural thrombi in the left ventricle was the most frequent type. In a few cases the embolism was due to large thrombi in the aorta. Clinically, gangrene due to atherosclerosis was usually distinguished without difficulty, especially in the younger patients. Embolism rather than thrombosis was indicated by the sudden development of the gangrene and the associated heart disease. At autopsy the diagnosis was supported by the finding of mural thrombi in the left side of the heart and sometimes by the presence of infarction of some organ. Occasionally the distinction from thrombosis was uncertain.

Nondiabetic Atherosclerosis.—This group is of particular interest in the present discussion, since the purpose of this study is to determine the influence of diabetes on the development of atherosclerosis in the lower extremities. Of the 167 cases of gangrene in this group only 2 involved an upper extremity. There were 119 males and 48 females.

Diabetes was not completely excluded in a majority of these cases, but no patient had any clinical symptoms of diabetes. In about one-half the cases the record shows no sugar in the urine; in the other half the urine was not examined. In only a few cases were blood sugar, levels determined, and these were in the normal range. In about two thirds of the cases, pieces of pancreas were available for microscopic study, and these showed no hyaline islets. Likewise the kidneys showed no intercapillary glomerulosclerosis. Some of this group may

TABLE 3.—*Incidence of Arteriosclerotic Gangrene in Nondiabetic and in Diabetic Males*

Decade	Non-diabetic Males	Atherosclerotic Gangrene		Diabetic Males	Atherosclerotic Gangrene	
		Number	Per Cent		Number	Per Cent
10- 20	902	0	0	9	0	0
20- 30	1,900	0	0	11	1	9.1
30- 40	2,700	0	0	23	0	0
40- 50	4,450	3	0.07	46	5	10.9
50- 60	5,822	12	0.20	118	20	16.9
60- 70	5,977	27	0.46	194	48	24.2
70- 80	4,600	36	0.82	171	40	23.0
80-100	1,588	41	2.89	33	9	24.2
50-100	17,682	(33) 116	0.66	466	116	24.9

have been mildly diabetic, but if there is an error here, it is in underestimating the importance of diabetes in atherosclerotic gangrene.

Cases in which gangrene occurred, whether of the nondiabetic or the diabetic group, are listed as cases of gangrene even though only the toes were gangrenous; but in the vast majority the gangrene was extensive and involved one or both legs.

Diabetic Atherosclerosis.—In tables 3 and 4 nondiabetic and diabetic patients are compared with respect to the incidence of gangrene due to atherosclerosis. Of 17,682 nondiabetic males over 50 years of age, 116 had gangrene due to atherosclerosis, an incidence of 0.66 per cent. Among 466 diabetic males over 50 years of age there were 116 with atherosclerotic gangrene, an incidence of 24.9 per cent. Atherosclerotic gangrene is therefore thirty-eight times as frequent in diabetic as in nondiabetic males. If one includes the 33 cases of gangrene due to embolism and acute arteritis, the total number involving nondiabetic males over 50 years of age would be 149, an incidence of about 0.8 per

cent. Gangrene is thirty-one times as frequent in diabetic males even when the nondiabetic patients with gangrene due to embolism and thrombosis are included. It is noteworthy that 41 of the 116 patients with atherosclerotic gangrene in the nondiabetic group were men over 80 years of age. When all forms of gangrene are included except those due to trauma and frostbite it appears that there is nearly an even chance that an adult male with gangrene of a lower extremity has diabetes.

Among 8,109 nondiabetic females (table 4) over 50 years of age there were 48 who had gangrene due to atherosclerosis, an incidence of 0.59 per cent. Among 499 diabetic females over 50 years of age there were 119 with gangrene of this type, an incidence of 23.8 per cent. Atherosclerotic gangrene is about forty times as frequent in diabetic as in nondiabetic females. If one includes the 29 patients whose gangrene

TABLE 4.—*Incidence of Arteriosclerotic Gangrene in Nondiabetic and in Diabetic Females*

Decade	Nondiabetic Females	Atherosclerotic Gangrene		Diabetic Females	Atherosclerotic Gangrene	
		Number	Per Cent		Number	Per Cent
10- 20	799	0	0	12	0	0
20- 30	1,581	0	0	39	0	0
30- 40	1,841	0	0	36	0	0
40- 50	1,156	0	0	51	3	5.9
50- 60	2,467	7	0.28	136	23	14.7
60- 70	2,583	17	0.67	201	55	27.3
70- 80	2,205	19	0.86	130	35	27.1
80-100	914	5	0.55	33	6	18.2
50-100	8,169	(29) 48	0.59	499	119	23.8

was due to embolism and acute arteritis, the total number of nondiabetic females over 50 years of age with gangrene would be 77, an incidence of about 0.95 per cent. Gangrene is twenty-five times as frequent in diabetic as in nondiabetic females even when the cases caused by thrombosis and emoblism are included. There is, therefore, more than an even chance that an elderly female with gangrene has diabetes.

SUMMARY

One may conclude that atherosclerosis of the lower extremities is an aging process that may lead to gangrene in advanced life in nondiabetic subjects but that the diabetic state intensifies and accelerates the gangrene due to this aging process to an astonishing degree. If only the gangrene due to atherosclerosis is considered, then gangrene develops nearly forty times as frequently in diabetic as in nondiabetic subjects. If all forms of gangrene of the legs except those due to trauma and frostbite are considered, nearly one half of the males and nearly two

thirds of the females with gangrene have diabetes. Gangrene develops with about the same frequency in males and in females, but since there are twice as many diabetic women as diabetic men, gangrene appears more frequently associated with diabetes in women.

In about two thirds of the diabetic persons in whom gangrene of a lower extremity developed it was the immediate cause of death. In the remaining one-third, death was due to some other cause, usually coronary disease.[1] Many patients survived amputation for months or years.

The percentage of diabetic persons in whom gangrene developed was somewhat less in the preinsulin era than in recent years, because there have not been so many deaths from coma since the discovery of insulin. Diabetic persons now live longer, and atherosclerosis is more frequent in older persons.

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1. Diabetes also accelerates atherosclerosis of the coronary arteries. About 4 per cent of deaths due to coronary disease in males and nearly 14 per cent in females are associated with diabetes (Clawson, B. J., and Bell, E. T.: Arch. Path. **48**:107, 1949).

FACTORS INFLUENCING THE FORMATION OF CARTILAGE IN THE HEALING OF EXPERIMENTALLY INDUCED FRACTURES

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NUMEROUS observations have been made on the regeneration of bone, especially in connection with the repair of fractures.[1] There is, however, considerable variation in the descriptions given by different authors with reference to the presence or the absence, as well as to the amount, of hyaline cartilage present in healing fractures. No satisfactory answer has been given to the question of the significance of its presence or absence.

Wieder [2] observed cartilage in the callus in all his experiments on complete fractures, rabbits and dogs being used. In the case of dogs, some attempt was made to immobilize the complete fractures, since a shaped wooden splint and a sodium silicate bandage were applied. He noted that the amount of cartilage present depended on the angularity and the mobility of the fragments and that it was always found in a wedge shape on the internal side of the angle. Wieder also observed an absence of cartilage in the healing callus of incomplete fractures produced with a longitudinal saw cut, dogs being used for the experiments.

In young adult rabbits Bast, Sullivan and Geist [3] found only small cartilaginous masses in the healing callus of incomplete fractures produced with a longitudinal saw cut. Its presence was infrequent and its development independent of the bony callus. The masses were always

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2. Wieder, H. S.: Univ. Penn. M. Bull. **20**:109, 136 and 204, 1907.

3. Bast, T. H.; Sullivan, W. E., and Geist, F. D.: Anat. Rec. **31**:255, 1925.

found in the young connective tissue at the cut ends of the fibrous periosteum outside the cambium. They never bridged the saw cut.

Using kittens, Blaisdell and Cowan [4] found cartilage in the healing callus of all complete fractures of the right humeri. Enneking,[5] Downs and McKeown [6] and Urist and McLean [7] noted cartilage in the callus of all complete fractures in rats; they made no attempt to immobilize the fractures.

In the reported experiments animals of different species and of varying ages have been used, and, as far as can be determined, the only comparable factor is the completeness or the incompleteness of the fracture, the latter represented by a saw cut.

The experiments which we shall describe were undertaken to determine whether such factors as species of animal, age, type of fracture (complete or incomplete) or mobility might be significant in determining the formation of hyaline cartilage in healing fractures.

METHOD

Three species of animals were used: white rats of the Sprague-Dawley strain, New Zealand white rabbits and guinea pigs. All were kept on diets considered to be adequate for these animals under laboratory conditions. The rats, whose ages were known, were divided into three groups—young, middle-aged and old. The rabbits and the guinea pigs, whose exact ages were not known, were classified into three groups according to weight, since weight gives a rough indication of the age.

A total of 88 white rats was used. The young rats ranged in age from 30 to 38 days, those of medium age from 75 to 80 days, and the older rats from 291 to 294 days. Thirty-nine white rabbits were divided according to weight as follows: The young rabbits weighed from 292 to 398 Gm., those of medium age from 2,458 to 3,305 Gm., and the aged rabbits from 7,580 to 8,723 Gm. Twenty-seven guinea pigs also were divided according to weight. The young ones weighed from 160 to 190 Gm., those of medium age from 415 to 500 Gm. and the older guinea pigs from 880 to 960 Gm.

All experimental procedures were performed with the animals under open drop ether anesthesia or intravenous or intraperitoneal thiopental sodium U. S. P. anesthesia.

One third of the animals in each of the three age groups were subjected to complete fracture of the midportion of the tibia of the right hindleg. To produce the fracture the right tibia was grasped firmly between the tips of index finger and thumb and bent laterally until the bone snapped; the broken ends of the shaft were then realined in as normal a position as possible. No attempt was made to immobilize the fracture.

4. Blaisdell, F. E., and Cowan, J. F.: Arch. Surg. **12**:619, 1926.
5. Enneking, W. F.: Anat. Rec. **101**:515, 1948.
6. Downs, W. G., Jr., and McKeown, R. M.: Arch. Surg. **25**:94, 1932.
7. Urist, M. R., and McLean, F. C.: J. Bone & Joint Surg. **23**:1 and 283, 1941.

Another third of the animals in each of the three age groups had the tibia of the right hindleg fractured in a similar manner. The fracture was immobilized by placing the leg in a plaster cast which extended to the hip joint and below the ankle joint so that only the tips of the toes were visible.

The remaining third of the animals in each of the three age groups were each given an incomplete fracture of the midportion of the shaft of the tibia of the right hindleg. The following procedure was carried out with sterile precautions. A thin circular saw, 4.5 cm. in diameter, was used, and a longitudinal cut—10 to 14 mm. in length in rats, 12 to 24 mm. in length in rabbits, and 12 to 16 mm. in length in guinea pigs—was made in the midportion of the shaft of the bone, parallel to its long axis. It is evident that the saw cut involved considerably more of the shaft of the bone in a rat than in a rabbit. The muscles were approximated over the area of the saw cut by interrupted plain catgut sutures, and the skin was closed by interrupted black silk sutures. No attempt was made to immobilize the fracture.

All fractures were permitted to heal, and animals from each age group were killed after varying intervals of time. Segments of bone were removed from the site of the fracture, fixed in Bouin's solution and decalcified in 5 per cent nitric acid. Several sections of each fracture were prepared, stained with hematoxylin and eosin and examined histologically.

RESULTS

The histologic picture of the fractures will not be described in detail here; particular attention was given to the amount of hyaline cartilage present in the sections obtained from each animal, and this is shown in the table.

Rats.—Cartilage was found in the healing callus of the completely fractured tibias after four days and was somewhat more abundant in the fractures which had been immobilized with plaster casts. It was still present twenty-eight days later. The cartilage was usually situated beneath the periosteum in and about the fracture. In the incomplete fractures produced with the saw, only minimal to moderate amounts of cartilage were present. The cartilage was located beneath the periosteum adjacent to the line of fracture, was seen as early as the sixth day and in the animals examined had disappeared by the twenty-first day. It should be noted that the same size circular saw was used on the rats as was used on the rabbits and the guinea pigs. Therefore, a greater proportion of the total circumference of the shaft was injured; this might explain the greater amount of cartilage in rats in contrast with the rabbits and the guinea pigs treated in a similar manner.

Rabbits.—Extensive amounts of cartilage were observed in the healing calluses of all complete fractures whether the legs had been immobilized or not. The cartilage was observed as early as the fourth day after the fracture. Cartilage was found infrequently (5 of 13 rabbits) and in small amounts in the healing callus of incomplete fractures produced with the saw. When present, it occurred as small islands located at some distance from the line of fracture.

Guinea Pigs.—Moderate amounts of cartilage were present in the healing calluses of all complete fractures when the legs were not immobilized. With immobilization, however, cartilage was present in the healing callus in only 4 of 9 animals and in minimal amounts, and it occurred as small islands located at some distance from the line of fracture. No cartilage was seen in the healing callus of any of the incomplete fractures produced with the saw.

Amounts of Cartilage Observed in Callus in Experimental Fractures

Days After Fracture	Complete Fracture			Complete Fracture and Plaster Cast Immobilization			Incomplete Fracture Produced with Longitudinal Saw Cut		
	Young	Middle-Aged	Old	Young	Middle-Aged	Old	Young	Middle-Aged	Old
Rats									
2	0	0	0	—	—	—	0	0	0
4	0	0	0	0	0	+	0	0	0
5-6	+	+	+	2+	3+	3+	+	+	+
7-8	2+	2+	2+	3+	3+	3+	2+	2+	+
9-10	3+	3+	3+	3+	3+	3+	2+	2+	2+
11-12	3+	3+	3+	3+	3+	2+	+	+	2+
15	2+	2+	2+	2+	2+	2+	2+	+	2+
19-20	2+	2+	2+	2+	2+	2+	0	+	0
23-24	2+	2+	2+	2+	2+	2+	0	0	0
28	2+	—	2+	2+	2+	2+	0	—	0
Rabbits									
4	2+	2+	—	2+	2+	—	0	0	—
6	3+	2+	—	3+	3+	—	0	2+	—
8	3+	3+	3+	3+	2+	2+	+	0	0
10	3+	3+	3+	2+	3+	2+	0	2+	+
13	2+	3+	3+	2+	2+	2+	2+	0	0
Guinea Pigs									
7	2+	2+	2+	+	+	0	0	0	0
9	2+	2+	2+	0	0	0	0	0	0
11	2+	2+	2+	0	+	+	—	0	0

\+ = Minimal amount of cartilage: small islands, each of which occupied up to one sixth of a high power field.
2+ = Moderate amount of cartilage: each island filled up to 1 low power field.
3+ = Extensive amount of cartilage: most of the islands exceeded the area of 1 low power field.

INFLUENCE OF AGE, SEX, SPECIES AND OTHER FACTORS

Age.—When fractures of comparable rats, rabbits or guinea pigs are examined from the standpoint of the presence or the absence of cartilage, it is very evident, as shown in the table, that there is no significant difference between the young, the middle-aged and the old animals.

Sex.—Male and female animals were used in these experiments, but sex did not appear to be a factor in this connection.

Species.—Although cartilage was observed in the fractures of the three species used, there was considerable variation in amount of

cartilage in the three species. It occurred most frequently in the rats, next in the rabbits and was rather an inconspicuous feature in the guinea pigs. In fact, no cartilage was observed in the incomplete fractures of this species. Such an observation emphasizes the importance of selecting the appropriate species for certain experiments and also the dangers of making generalization from experimental observations on one species. It is entirely possible that if such studies were extended, there would be individual differences within various strains of the same species.

Other Factors.—The factor of diet was beyond the scope of this experiment, and because each species of animal was of necessity on a different diet, it is not inconceivable that this factor may be of some importance. Since cartilage was present in the healing calluses of all animals with complete fractures when the involved legs had not been immobilized and was present in the calluses of all animals with complete fractures when the legs had been immobilized with plaster casts except that when guinea pigs were used cartilage was present in only 4 of the 9 animals and in minimal amounts, it would appear that there is here a species difference.

The presence of only small islands of cartilage, and those infrequently, in the callus of incomplete fractures produced with the saw would seem to indicate that the type of fracture and the mobility of the fragments determine to a large extent the amount of cartilage present in the callus. Whereas a plaster cast tends to hold the fractured fragments in normal alinement, it cannot immobilize these fragments.

SUMMARY AND CONCLUSIONS

The type of fracture—that is, complete or incomplete—determined to a large extent the amount of cartilage present in the callus of healing fractures.

No difference was noted in the amount of cartilage in immobilized as contrasted with nonimmobilized complete fractures except in the guinea pigs, in which the difference was conspicuous. This suggests that under conditions such as were present in this experiment mobility probably contributes to the amount of hyaline cartilage found in a healing callus.

Age did not appear to influence this determination.

The amount of cartilage observed in healing fractures varied considerably in different species.

THE RICKETTSIAL DISEASES: DISCOVERY AND CONQUEST

HOWARD TAYLOR RICKETTS AWARD LECTURE

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WE ARE here to initiate a series of lectures which will keep green the memory of Howard Taylor Ricketts, whom all admired and to whom, while he lived, many of us were drawn with deep affection. Hereafter, those who will be called on to fill this Ricketts award lectureship will bring to it the fruits of personal efforts to advance the sciences on which medicine depends, and will receive this Ricketts medal as a token of their having been fraternally associated with him in that band of laborers in God's harvest concerned with human welfare. Like Ricketts, for he was only 39 years old when he died, most of them will be in the prime of life; but to initiate this lectureship, Dr. Ludvig Hekton has been chosen, together with your essayist. Our selection undoubtedly depended in the main on our having been, in former years, closely associated with him whom we would honor.

Dr. Hektoen, in 1905 head of the department of pathology and bacteriology of the University of Chicago, was attracted by Ricketts' earliest researches on blastomycosis [1]; this was one of the first diseases shown to be produced in man by a yeastlike organism. Recognizing Ricketts' ability as an investigator, Dr. Hektoen suggested to Ricketts that he spend some time in the Pasteur Institute in Paris and then join him in his department. I suspect also that Dr. Hektoen had a hand in the invitation received by Ricketts soon thereafter to prepare a series of articles on the subject of immunity for *The Journal of the American Medical Association*. The material of those articles, after revision and with some additions, was published as a book in 1906.[2] Students who entered the medical school about that time, as I did, were fascinated by this book. Perhaps it was an even greater stimulus to

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The first Howard Taylor Ricketts Award Lecture, University of Chicago, Chicago, May 23, 1949.

1. Contributions to Medical Science by Howard Taylor Ricketts (1870-1910), published as a tribute to his memory by his colleagues under the auspices of the Chicago Pathological Society, Chicago, The University of Chicago Press, 1911.

2. Ricketts, H. T.: Infection, Immunity and Serum Therapy, ed. 1, Chicago, American Medical Association Press, 1906.

the man who wrote it; writing often is like that. In any case, in 1906 or thereabouts, when his mind was filling with this accumulated information, Ricketts' interest was attracted and his imagination stirred by reports of a disease which, like plague and typhus fever, was characterized by small cutaneous hemorrhages (petechiae), causing spotting of the skin. The disease was known as "Rocky Mountain spotted fever" and prevailed in Montana and adjacent states. Plague, as he had written in his book, occasionally caused spotting of the skin. Plague had ravaged the Roman Empire in the sixth century, had destroyed half of the population of the eastern provinces, had swept over Europe under the name of the Black Death in the fourteenth century, had killed millions and had only recently been controlled by rigid quarantine. Kitasato [3] and Yersin,[4] working independently in the Hongkong epidemic of 1893, each discovered that the cause of it was a minute bipolar microbe, which was oval shaped, with the two poles staining deeply. Guinea pigs died of plague when material containing the organism was rubbed into incisions in the skin or even onto the unbroken skin. The Report of the Indian Plague Commission [5] had shown that rats harbored the disease and that the usual means by which it was transmitted from rat to rat and from rat to man was by the flea. This discovery had led to effective control, and thereafter major epidemics of plague had been prevented.

Typhus resembled plague in several aspects. It, too, caused spotting of the skin. Previously it had been confused with typhoid fever, but an American physician, Gerhard,[4] in 1837 pointed out the clinical and pathologic differences between the two. The bacillus of typhoid had been described by Eberth [5] in 1880 and was cultured in 1884 by Gaffky.[5] The cause of typhus remained unknown, which meant that epidemics of the disease continued to be a major threat to humanity. Throughout late European history typhus had accompanied poverty and human desolation almost everywhere. It accompanied famine. It was found in jails. It followed armies in almost every war. In the siege of Granada in 1489 the Castillian army under Ferdinand and Isabella lost six times as many men from typhus as were killed by the Moors. In 1528 the French army in the siege of Naples lost a victory over Charles V because of typhus, an event which may have changed the course of history. Likewise, in the sixteenth century armies assembled for combating the Turks were decimated by this disease. The disaster which befell Napoleon when he invaded Russia in 1812 was in part the

3. Cited by Ricketts.[2]

4. Gerhard, W. W.: Am. J. M. Sc. **19**:289, 1837.

5. Cited by Smith, D. T., and others: Zinnser's Textbook of Bacteriology, ed. 9, New York, Appleton-Century-Crofts, Inc., 1948, p. 475.

work of typhus, and so on and so on; the record is terrific. It was graphically related not long ago by Zinsser [6] in his book "Rats, Lice and History." However, typhus epidemics in 1906 were few and relatively less severe than they had been. Annual epidemics occurred in Mexico, but Mexico was relatively distant; whereas a comparably deadly disease, "spotted fever," was present just around the corner in Montana.

I mention these diseases now, plague and typhus, because Howard Ricketts had them in his mind as possibly related in their causation and possibly related also to Rocky Mountain spotted fever, when on April 21, 1906, as he wrote, he "arrived in Missoula, Montana, equipped for the bacteriologic and hematologic study of so-called Rocky Mountain (spotted) fever and for the study of infectious agents by means of animal inoculations." He was abetted and encouraged in this adventure by Dr. Hektoen, who later, in writing of this period, had this to say, (the quotation is from Thomas Goodspeed [7]):

> As we follow the various stages of the progress of this intensely active work (with spotted fever) it becomes very clear that Dr. Ricketts not only was gifted with imaginative powers so that he could see and trace the various lines along which the solution of a problem might be sought, but that he also possessed in a full measure the capacity for that hard, accurate, patient work necessary for the more difficult task of finding the one true solution. This combination of speculative ability and the power to do steady toil, even drudgery, often under great difficulties, made him a great investigator and brought him success.

The investigations of Rocky Mountain spotted fever made by Ricketts in the field (Montana) and in his laboratory at the University of Chicago led in 1906 to its being transmitted to experimental animals (guinea pigs and monkeys) by inoculation of the blood of patients and also by the bites of wood ticks which previously had been infected experimentally. They led in 1907 to the discovery that the infection could be transmitted through the eggs to the offspring of ticks and to the further discovery of infected ticks in nature—on the west side of the Bitter Root Valley near Missoula, where the disease prevailed more fiercely. The wood tick then was the vector, the carrier of the disease. The investigations also led to discovering that blood serum of infected animals or patients when passed through Berkefeld filters (filters made of diatomaceous earth) lost its virulence, which meant that the infectious agent must be of sufficient size to be visible with the microscope. In 1909 the studies led to the following report: "Since the spring and summer of 1906, bodies which I have referred to in my notes as 'dipplococcoid bodies' and sometimes short bacillary forms have been found with considerable constancy in the blood of guinea pigs and

6. Zinsser, H.: Rats, Lice and History, Boston, Little, Brown, & Company, 1935.

7. Goodspeed, T. W.: Howard Taylor Ricketts, The University Record, Chicago, University of Chicago Press, 1922, vol. 8, p. 110.

monkeys which were infected with Rocky Mountain spotted fever." He had also found these bodies in the blood of patients, and in the winter of 1907-1908 eggs from infected ticks crushed on cover glasses, fixed in alcohol and stained with Giemsa stain were seen, and again I quote from his report: ". . . to be laden with astonishing numbers of an organism which appears typically as a bipolar bacillus of minute size. . . . The salivary glands, alimentary sac and ovaries of infected female ticks were literally swarming with exactly similar micro-organisms which on the contrary appeared to be entirely absent from the viscera of the uninfected tick." The organisms failed to grow on any culture medium, but striking evidence of their probable etiologic relationship to Rocky Mountain spotted fever was found in the positive outcome of agglutination tests made with the eggs of infected ticks. The organisms were so numerous in the eggs that a suspension of them thick enough for such a test could be made by crushing 40 to 50 eggs in a drop of salt solution. When serum of normal guinea pigs was added to this suspension, in proportions of 1 to 1 up to 1 to 20, it caused at most a slight agglutination (clumping) of the organisms. There was no clumping at higher dilutions. On the other hand, when the serum of animals which had recovered from the disease was added to the suspensions, it provoked complete agglutination (clumping) in dilutions up to 1 to 320 and even, in some instances, in dilutions as high as 1 to 1,000. Then again, in 1909, Ricketts could report that successful vaccination of experimental animals had been accomplished by injection of the tissues and eggs of virulent ticks, ticks rich in "bacilli" after the material had been sterilized either by desiccation or by chloroform.

At this point came a setback. Scientific proof would seem to demand that the organisms described be found constantly in all ticks capable of transmitting the disease and that it be absent constantly from all nonvirulent ticks, but, when more ticks had been collected, the "bacilli," as Ricketts then called them, were often found in great abundance in both eggs and tissues of ticks which were shown experimentally to be absolutely incapable of transmitting the disease. Furthermore, these "bacilli" responded to the specific agglutination test in the same manner; that is to say, they were clumped by immune "spotted fever" serum in high dilutions and by normal serum not at all or only in low dilutions of 1 to 10 or 1 to 20. Here was an acid test of the scientific genius of Howard Ricketts. In the first place, many men would have been satisfied with the early observation that the micro-organisms were not present in uninfected ticks and would not have proceeded, as he did, to collect more ticks to prove the point conclusively. In the second place, many men finding the "bacilli" in the uninfected ticks would have lost their faith in the significance of the earlier observations. Not so Ricketts, whose thoroughness and demand for accuracy

were illustrated by his search for further evidence and whose imaginative power was shown by his subsequent analysis of this apparent paradox. Actually, as the later work of other investigators has conclusively confirmed, the organism now called "the Rickettsia of Rocky Mountain spotted fever" is a common parasite of many varieties of ticks, and lives symbiotically without injury to its host, the tick. In this respect it differs from the Rickettsia of typhus, which is fatal to the louse. Ricketts reasoned that the organism in question, although the true cause of Rocky Mountain spotted fever, had a tendency to undergo a loss of virulence as a consequence of long residence in the tissues of the tick alone, assuming virulence only under such conditions as involved its frequently being passed through some suitable animal. With Dr. Josiah Moore, then his assistant, he previously had found a number of wild rodents, notably the ground squirrel, the ground hog and the rock squirrel, to be suscepible to Rocky Mountain spotted fever, and assumed correctly that the usual animal involved was one or more of these wild animals. He pointed out that scarcely any fact is better known among bacteriologists than that pathogenic organisms lose their virulence for a host if they do not occasionally pass through the host, and concluded that such periodic residence was necessary for the maintenance of the virulence of the organism responsible for "spotted fever."

From his work with Rocky Mountain spotted fever, Ricketts was more convinced than ever that typhus was related in some way to plague and "spotted fever." He furthermore was confident that the methods of attack which he had learned in his work on the latter would disclose the cause of typhus and the method of its transmission. It, like "spotted fever" and the plague, was an exanthem that is provocative of intracutaneous hemorrhages, and many facts already known about the spread of typhus from one victim to another suggested that it, unlike measles or smallpox, but like Rocky Mountain spotted fever and the plague, was transmitted by some insect vector. He had in mind the louse. Again Dr. Hektoen appeared on the scene and made arrangements in the spring of 1909 for Dr. Ricketts to obtain a leave of absence from the University of Chicago and for the expenses of a study to be made in Mexico on typhus fever.

Since the annual epidemics of Mexican typhus usually started in late autumn, Ricketts planned to leave for Mexico in the autumn of 1909. He actually arrived in Mexico City early in December of that year, to learn, only after his arrival, that others, following exactly the same procedures that he had planned to institute, already had succeeded in transmitting the disease to the monkey: Nicolle[8] in Tunis, Africa,

8. Nicolle, C.: Compt. rend. Acad. de sc. **149**:157, 1909.

and Anderson and Goldberger,[9] in Mexico. Nicolle, indeed, after first infecting a chimpanzee by injecting the blood of human patients, had infected lower apes (Macacus sinicus) with the blood of the chimpanzee and then had transmitted the disease from one Macacus to another by means of the body louse (Pediculus vestimenti). Anderson and Goldberger had transmitted the disease to lower apes directly by injecting the blood of patients. To be thus forestalled was a bitter disappointment. However, much still needed doing, in particular the discovery of the infectious agent transmitted by the louse and causing the disease. He set to work. Five reports,[1] all but the last published before his death in May 1910, testify to his accomplishments. The first confirmed the observations that the disease could be transmitted to the ape by injection of the blood of patients, and added the further information that the serum of such blood lost its virulence when passed through Berkefeld filters. The second report related to transmission of the infection by lice, both from man to monkey and from monkey to monkey. One monkey was infected by the introduction of the feces of infected lice into small incisions in the skin. The last finding is of importance, for the later work of many other investigators has led to the conclusion that the usual method of infection of the human being is by the feces of the louse. The insect bites and, at the same time, defecates. The bite provokes some itching and the victim, by scratching, rubs the feces into the tiny wound created by the bite. The third report, the most important and entirely original, dealt with the description of an organism seen in blood and lice. The filtration experiment, which had been confirmed by Anderson and Goldberger,[10] had provided evidence that the micro-organism was of such a size as to be visible with the microscope, and now in preparations of blood of patients taken from the seventh to the twelfth day of the disease and stained with Giemsa's stain, short bacillary germs were seen, which, as Ricketts then expressed it, were roughly of the appearance of those which caused the "hemorrhagic septicemia group" of diseases, namely, plague and Rocky Mountain spotted fever. The micro-organism usually appeared to stain solidly, but on minute examination an unstained or faintly stained bar was seen to extend across the middle. "Certain other bodies," as he wrote, "the identity of which is not so clear, may represent degeneration or involution forms of the above. They consist of two stained granules connected by an 'intermediate substance' which is stained faintly blue or not at all. Frequently one of these granules or 'poles' is larger than the other and stained a deep purple, whereas the smaller (granule) takes a faint blue color." Similar structures were regularly observed in

9. Anderson, J. F., and Goldberger, J.: Pub. Health Rep. **24**:1941, 1909.
10. Anderson, J. F., and Goldberger, J.: Pub. Health Rep. **25**:177, 1910.

unstained preparations of fresh blood. Likewise, polar staining organisms (like those observed in the blood) were present almost constantly and often in large numbers in infected lice. Similar bodies were found, but only occasionally and in small numbers, in the intestinal contents of uninfected lice.

The story of Ricketts' fatal illness from typhus acquired in Mexico, and of his death "on the firing line," needs no repetition here. Through these achievements Ricketts' name will live in history. His hemorrhagic septicemias under another name, his name, have come to include not only Rocky Mountain spotted fever and the epidemic typhus of his studies, but also a number of related diseases, such as the murine, flea-borne, form of typhus, established as a second variety of typhus by Dyer and associates,[11] who in 1931 isolated rickettsias from rat fleas in Baltimore; the tsutsugamushi fever of the Orient, which also is called "scrub typhus"; the Q fever, first reported from Australia but widespread in the world; and rickettsialpox which was very recently observed in one of the boroughs of New York. This is to mention only a few of the rickettsial diseases. These diseases, like the plague, are transmissible by arthropods, fleas, mites, ticks or lice. There are many more; however, missing in the current lengthy list is the plague with characteristics which, as I have said, originally led Ricketts to his conception that Rocky Mountain spotted fever and typhus were related to each other and to the plague. However, Ricketts may have been right in including plague in his group of arthropod-borne human hemorrhagic septicemias, now named the rickettsial diseases. Pinkerton,[12] a leading investigator in this field, has written recently that several organisms currently not classed with rickettsias are closely related to rickettsias, and that among these is the species Pasteurella, which includes Pasteurella tularensis, the cause of tularemia, a disease not known in Ricketts' day, and Pasteurella pestis, as the plague bacillus now is called. The rickettsias, by current definition, are obligatory parasites; that is, they owe their lives, like viruses, to other cells which they inhabit. In other words, they cannot live alone, even on culture mediums, but it is a curious system of classification, as Pinkerton wrote, which is based on the inability to prepare mediums containing suitable metabolites.

The name "Rickettsia" was given first to the organism causing typhus. Da Rocha-Lima,[13] of the Ship and Tropical Diseases Institute,

11. Dyer, R. E.; Rumreich, A., and Badger, L. F., cited by Snyder, J. C.: The Typhus Fevers, in Rivers, T. M.: Viral and Rickettsial Infections of Man, Philadelphia, J. B. Lippincott Company, 1948, p. 483.

12. Pinkerton, H.: The Classification of Rickettsiae and Rickettsial Diseases, in Moulton, F. R.: Rickettsial Diseases of Man, Washington, D. C., American Association for Advancement of Science, 1948, p. 70.

13. da Rocha-Lima, H.: Berl. klin. Wchnschr. **1**:567, 1916.

of Hamburg, Germany, studied an epidemic of typhus in the Polish town of Wloclawek at the beginning of the first World War and observed intracellular bodies in the intestinal lining of infected lice. These bodies were present also in the intestinal content of the lice, but serial sections of the lice showed them to be most abundant in the cells lining the intestine. From their appearance, these bodies gave da Rocha-Lima the impression of being bacteria. However, unlike bacteria, they stained poorly, they failed to grow on culture mediums and in certain stages of their development they resembled elementary corpuscles such as are seen in the inclusion bodies of diseases like smallpox, caused by viruses. Whatever they were, they differed enough from the known types of microbes to suggest to da Rocha-Lima that they might be a *besondere Gattung*, that is, a separate genus or species. The question could not be settled without further study; so, in the meantime, he suggested it would be the part of wisdom to choose for them a noncommittal name. Therefore, he proposed to name these organisms "Rickettsia-Prowazeki" in honor of Ricketts and of his (da Rocha-Lima's) colleague, von Prowazek, who like Ricketts had lost his life in research on typhus.[14] The name stuck, as applied to typhus, and later, when new diseases were discovered in relationship to typhus, the name "Rickettsia" became the general designation for this group of organisms, which by definition are between bacteria and the larger viruses, their in-between position depending both on size and on degree of parasitism. Like the viruses, they grow within the cells of other organisms, whereas in size and shape they resemble the bacteria.

Thus far, this discussion has been confined to the discovery of the rickettsias. The present time is very fitting for this review, because even now, and I mean within the last twelve months, some forty years since the pioneers—chief among them, Howard Ricketts—discovered the first of them, an effective cure has been developed for nearly all of the diseases which they cause, including Rocky Mountain spotted fever and typhus.

First, however, let us turn to methods of prevention of epidemic typhus, which depended for their effectiveness on the discovery of Nicolle, confirmed by Anderson and Goldberger and Ricketts and Wilder, that epidemic typhus could be transferred by lice. Methods of delousing were introduced immediately on the outbreak of World War I. In Europe, typhus had subsided in the last half of the nineteenth century, but it reappeared again in Russia, in Poland and in Serbia with the onset of the war. In less than six months, in 1914, more than 150,000 deaths occurred in Serbia, yet the epidemic there was effectively suppressed by bathing the people and delousing their clothes with

14. da Rocha-Lima, H.: Arch. f. Schiffs- u. Tropen-Hyg. **20**:17, 1916.

steam. Similar measures applied on the western front were undoubtedly responsible for the avoidance of an epidemic there in World War I. However, bathing and steaming were time consuming, also expensive, and without lasting effects. In World War II, DDT (dichlorodiphenyltrichloroethane) became available, and delousing with it was dramatically successful. This was demonstrated first in the epidemic in Naples, in 1943 to 1944, and later, very strikingly, when the allied armies entered Germany.

Although epidemics had thus become preventable through delousing, protection of persons exposed to endemic infections, such as murine typhus, tsutsugamushi fever (scrub typhus) and Rocky Mountain spotted fever, and of persons working in laboratories demanded vaccination. But how were vaccines to be made of organisms that refused to grow on artificial mediums? Answers came from several workers but the most practical one was that of H. R. Cox,[15] who in 1938, working in Hamilton, Mont., found that he could culture rickettsias in the yolk sacs of fertile hens' eggs and from these cultures make effective vaccines both for Rocky Mountain spotted fever and for typhus. The living cells of the membranes and the yolk sac of the developing chick embryo, as had first been shown by Goodpasture,[16] provide the necessary medium for cultures of viruses, which, like Rickettsia, as I have said before, can grow and multiply only in the living cell. A field test carried out in Cairo, Egypt, by the American Typhus Commission proved the value of the Cox type of vaccine, and this vaccine later was produced on a tremendous scale and administered to several million troops. By delousing combined with vaccination, the mortality from typhus fever in World War II was reduced almost to zero. Of the American troops in Africa and Europe only 64 became infected, and all of them recovered.

Until the last twelve months, however, there still remained the therapeutic problem, the problem of how to cure a person once he had acquired typhus or any other of the several rickettsial diseases. No form of treatment had been of much advantage in any of these diseases, and the mortality of Rocky Mountain spotted fever and of typhus was as high as 20 to 40 per cent and even higher. Chemotherapy, the administration of the sulfonamides, so dramatically effective against most of the bacteria, proved to be of no advantage against rickettsias. Sulfonamides likewise were ineffective against the viruses. Then came the antibiotics, chemicals obtained from soil bacteria and molds. One of them, penicillin, was even more successful in the treatment of most

15. Cox, H. R.: Pub. Health Rep. **53** (pt. 2):2241, 1938.

16. Goodpasture, E. W., and Buddingh, G. J.: Chick-Embryo Technics, in Rivers, T. M.: Viral and Rickettsial Infections of Man, Philadelphia, J. B. Lippincott Company, 1948, p. 97.

bacterial diseases than the sulfonamides had been, but again, with few exceptions, notably psittacosis (parrot fever), penicillin, and after it the antibiotic streptomycin, proved to be of no advantage in diseases caused by viruses and rickettsias. However, the results obtained in those diseases in which penicillin and streptomycin were effective kept hopes high and led to a frantic search for other antibiotics. It is supposed that the number of these already found to be effective in one or another infectious disease is around one hundred, and at long last not one but two have been developed which attack not only bacteria but also rickettsias and some viruses. Study by Duggar [17] of 3,400 strains of fungus-like organisms or molds obtained from soil at last yielded aureomycin, so named because of the golden color of colonies of the mold. This was shown by Wong and Cox,[18] the same Cox who made the vaccine, to protect guinea pigs and mice infected with typhus, Rocky Mountain spotted fever, Q fever and rickettsialpox. The other effective agent is chloromycetin® which was cultured from another fungus-like organism isolated by Ehrlich and associates [19] from a soil obtained in Venezuela. It more recently has been synthesized and now is named chloramphenicol. Reports of successful treatment of patients with chloromycetin® and aureomycin are currently arriving from all sides. For example, in Bolivia, Payne and his associates [20] successfully treated epidemic typhus with chloromycetin® and in Maryland, where the usual mortality from the eastern form of Rocky Mountain spotted fever has been 20.8 per cent, 15 patients treated with chloromycetin® were freed from fever in an average of 2.2 days. They were patients of my classmate, Dr. Maurice Pincoffs,[21] who was exposed as I was in 1907, 1908 and 1909 to the influence of Howard Ricketts. Pincoffs many years ago found that Rocky Mountain spotted fever had become endemic in eastern Maryland. In Baltimore, also, Schoenbach [22] treated successfully with aureomycin a patient presenting the characteristic clinical picture of recrudescent typhus (Brill's disease) and in Guadalajara, Mexico, Knight and a group of clinical investigators [23] from the University of Guadalajara and from Cornell University Medical College administered aureomycin to 11 patients with typhus (presumably

17. Duggar, B. M.: Ann. New York Acad. Sc. **51**:177, 1948.

18. Wong, S. C., and Cox, H. R.: Ann. New York Acad. Sc. **51**:290, 1948.

19. Ehrlich, J.; Bartz, Q. R.; Smith, R. M.; Joslyn, D. A., and Burkholder, P. R.: Science. **106**:417, 1947.

20. Payne, E. H.; Knaudt, J. A., and Palacios, S.: J. Trop. Med. **51**:68, 1948.

21. Pincoffs, M. C.; Guy, E. G.; Lister, L. M.; Woodward, T. E., and Smadel, J. E.: Ann. Int. Med. **29**:656, 1948.

22. Schoenbach, E. B.: J. A. M. A. **139**:450, 1949.

23. Knight, V.; Ruiz-Sanchez, F.; Ruiz-Sanchez, A., and McDermott, W.: Am. J. Med. **6**:407, 1949.

murine), and in every instance obtained both control of the disease and complete recovery. Comparably encouraging clinical reports now are numerous enough to indicate, without a question of a doubt, that the cure for the "human hemorrhagic septicemias," to use Howard Ricketts' term, has been found.

This discovery of a cure for the rickettsial diseases represents the final chapter of an epic. I have told how Howard Ricketts, as early as 1906, was led to consider Rocky Mountain spotted fever, plague and typhus as related; how his work with Rocky Mountain spotted fever led to his discovery of the micro-organism which causes that disease, and how in Mexico, in 1910, in the blood of typhus patients and in infected lice, he observed a micro-organism which in size, structure and staining reactions resembled that of Rocky Mountain spotted fever. Thus began the war against rickettsial diseases. Ricketts' studies further disclosed that Rocky Mountain spotted fever was transmitted by the tick, and the emphasis placed by him on the possible existence of a group of insect-transmitted human hemorrhagic septicemias, including typhus, paved the way to the discovery that typhus was transmitted by the louse and led to the development of a method for preventing epidemics of a disease which for many centuries had been a scourge like the plague. Later to witness the conquest of typhus epidemics by prevention was a privilege, and now at last to live to see a cure for typhus fever is a tremendous satisfaction, to those of us who worked with Howard Ricketts and for forty years have mourned his sacrifice.

Case Reports

ANGIOMA OF THE UTERUS

A Report of a Case of Submucous Polypoid Hemangioma of the Uterus

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BROOKLYN

ANGIOMA of the uterus is rare. This seems remarkable in the light of the innate vascularity of the uterus, the periodic vascular metamorphosis associated with the menstrual cycle and the tremendous increase in structure and function accompanying the pregnant state. It would seem likely that in the uterine organ, where the vessels are constantly undergoing degeneration and regeneration in continuously recurring cycles, occasionally undergoing prolific regeneration, and where infection is not infrequent, the circumstances would favor the development of a vascular tumor. Considering the large number of uteri examined by competent pathologists, the 15 true cases of angioma of the uterus recorded in the literature are few indeed.

The nomenclature used in describing vascular tumors is confusing in that many synonyms are in use and further in that identical terms signify various pathologic processes. It is therefore advisable to define and indicate the pathologic significance of the several terms employed.

An angioma is a neoplasm composed of newly formed endothelium-lined vessels, a hemangioma arising from blood vessels and a lymphangioma from lymph vessels. When the vascular channels are widely dilated and the connective tissue septums are thin, the angioma is designated as cavernous. The dilatation of the end vessels or capillaries is known as telangiectasis. Extensive development of vessels occurs in many tumors as a result of venous stasis or unusual demands for nutrition; yet these vessels present a normal structure. Such tumors are not angioma but are, as suggested by Ewing,[1] "angiomatosum." The term "endothelioma" in its broadest sense designates a tumor derived from the lining cells of blood vessels, lymph vessels, subdural spaces or serous cavities. Its meaning, however, has been modified by usage to indicate an additional invasive quality, primarily local, slow but progressive, and without true sarcomatous change.[1]

REPORT OF CASE

In December 1947 a 50 year old white woman was admitted to the Long Island Division of Kings County Hospital, with a chief complaint of vaginal bleeding, accompanied for the last five weeks by abdominal cramps. Two years

From the Departments of Pathology and Obstetrics and Gynecology, Kings County Hospital, Long Island Division, and Long Island College of Medicine.

1. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders & Company, 1940, pp. 249-385.

prior to admission in one of her menstrual periods the flow had been unusually heavy for the first two days and then had persisted for five weeks. After one week of respite the bleeding recurred and persisted until admission. Previous menstruation had been essentially normal. She had had three normal pregnancies and was treated for a postpartum hemorrhage during the delivery of her second child in 1933. Her last pregnancy, in 1937, was uneventful. The results of the general physical examination were not significant except for a large abdominal mass rising from the pelvis to within 4 cm. of the umbilicus. The mass was firm, movable and nontender. Pelvic examination revealed a parous introitus with relaxed anterior and posterior vaginal support. The cervix was high, posterior, soft, patulous, lacerated and not tender. The uterus was nodular, irregular, firm, and the size of a four month gestation. A diagnosis of fibromyoma uteri was made and total hysterectomy, bilateral salpingectomy and right oophorectomy were performed. At laparotomy the uterus was uniformly enlarged to the size of a three month gestation. The patient's postoperative course was uneventful, and she was discharged on the tenth hospital day.

The specimen consisted of a whole uterus with both tubes and the right ovary attached. The uterus was globular in shape and measured 12 cm. in length, 14 cm. in transverse diameter and 8 cm. in vertical diameter. The serosal surface was smooth and glistening, and on the posterior wall there were several superficial small hemorrhagic areas. Several subserosal nodules were seen, the largest measuring 1 cm. in diameter. The uterus was opened with a midline longitudinal incision. Several grayish white nodules were observed in the myometrium, the largest measuring 1.5 cm. in diameter. On section these nodules showed a whorl-like pattern. The uterine cavity was enlarged and filled by an inverted pear shape polypoid mass, measuring 9 by 6 by 5 cm., with a circular base at the upper portion of the posterior wall, measuring 3 cm. in diameter (fig. 1 *A* and *B*). The surface of the tumor was smooth, glistening, purplish blue in the distal half and yellowish in the proximal half. On section the cut surface of the proximal half had a yellowish color which merged diffusely into the myometrium at the base for a distance of 1.5 cm. The cut surface of the distal half was purplish blue and revealed numerous irregular cystic areas, the largest ones measuring about 0.5 cm. in diameter, presenting a honeycombed appearance. The endometrial surface of the uterine cavity was grayish white, smooth, thin and glistening, and multiple hemorrhagic areas were noted.

Microscopic examination of the uterus revealed the endometrium as a thin layer lined by columnar epithelium with oval nuclei centrally located in a pink cytoplasm. The stromal cells were large with oval nuclei in a pale pink cytoplasm. Edema and interstitial hemorrhage were observed in the stroma. The glands were widely separated, small, round or oval, occasionally dilated, and lined by columnar epithelium with oval centrally located nuclei in a dark pink cytoplasm. The myometrium was composed of smooth muscle fibers in orderly arrangement. There were several circular areas in which the fibers were in a whorl-like pattern, and hyaline changes were seen in these areas. The perimetrium consisted of a thick, fibrous connective tissue layer with fibrinous adhesive bands at the periphery and with hemorrhage underneath it.

The polyp revealed numerous thick-walled and thin-walled, vascular channels with a simple lining of endothelial cells, some flat and others high cuboidal (fig. 2). The vascular channels varied greatly in size and shape, and although many of them were empty, some were filled with blood. There were numerous

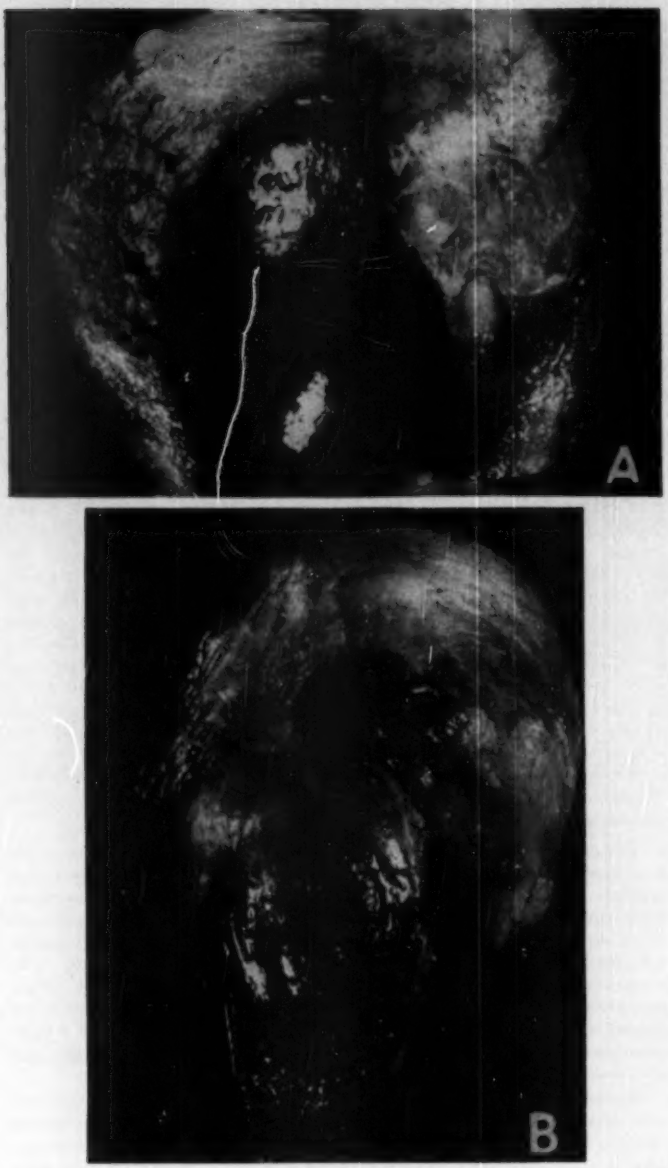

Fig. 1.—*A*, gross appearance of uterus with polyp—anterior view; *B*, gross appearance of hemisected uterus and polyp—lateral view.

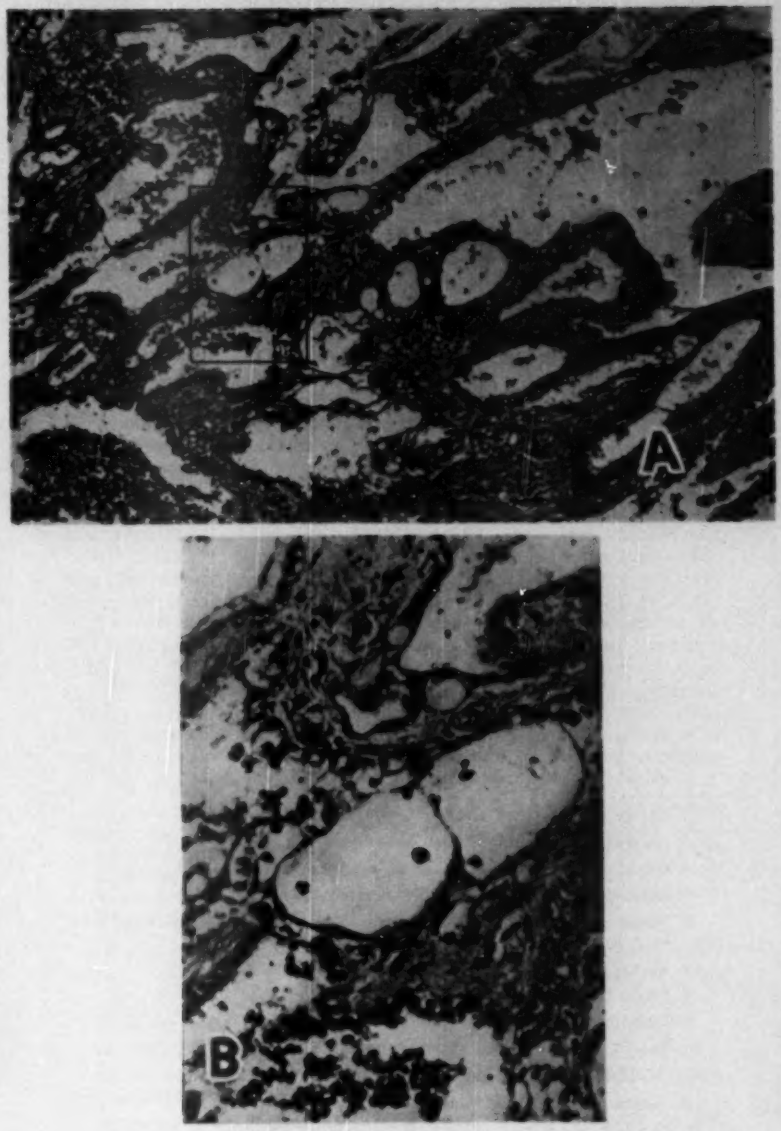

Fig. 2.—*A*, microscopic appearance of section of midportion of polyp. Note blood cells in the endothelium-lined spaces. *B*, microscopic appearance of the demarcated portion of *A*. Note varying type of endothelial lining of the different spaces.

large oval cells in these vascular channels, with round, heavy-staining nuclei in an abundant bright pink cytoplasm. The cytoplasm of these cells stained bright red with sudan III. The stroma consisted of connective tissue. There were numerous large cells in the stroma, with flattened nuclei located peripherally in a clear cytoplasm. These cells failed to stain with sudan III. At the base of the polyp the vascular channels were seen extending for a short distance into the myometrium. However, the endothelial cells showed no tendency toward hyperplasia, and only a rare mitotic figure. The endometrial lining of the uterus could be seen continuing a short way up the base of the polyp. The distal portion of the polyp had a thin, necrotic, unidentifiable tissue lining. Several portions of the distal half of the polyp showed necrosis.

REVIEW OF THE LITERATURE

Sporadically through the years there have been reports in which tumors of the uterus were described which had marked angiomatous elements. Three reports appeared in the literature describing the following types of tumors: ramifying angiomyoma,[2] fibromyoma angiomatosum [3] (3 cases) and leiomyosarcoma with ramifying angiomyoma.[4] Sufficient microscopic evidence was present to have classified these tumors as sarcoma. One tumor reported as hemangioma [5] was described as a recurring tumor of the uterus and pelvis with many intravascular extensions of tumor tissue. This might better have been called hemangioendothelioma to indicate its invasive quality. However, the reported ones, for the most part, have been fibromyoma with extensive development of the vascular elements. They have been given an assortment of names: telangiectatic myoma,[6] hamartoma angiofibrosum,[7] angiomyoma,[8] hemangiomyofibroma,[9] lymphangioendothelioma,[10] hemangiomyoma,[10a] hemangiomatous myofibroma [10b] and angiomyoma.[11] For obvious reasons the latter group of tumors merits one name. Since Ewing has suggested the term "angiomatosum" to indicate those tumors that have extensive development of vessels with normal structure, fibromyoma with overdeveloped vascular systems might best be called fibromyoma angiomatosum.

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2. Pusch, L. C.: Am. J. Obst. & Gynec. **24**:907, 1932.

3. Gardner, G. H.: Am. J. Obst. & Gynec. **40**:822, 1940.

4. Gnassi, A. M., and Price, H. P.: Am. J. Obst. & Gynec. **42**:514, 1941.

5. Kevorkian, A. Y.: New England J. Med. **223**:1, 1940.

6. Virchow, R.: Die Krankhaften Geschwülste, Berlin, A. Hirschwald, 1863-1867, vol. 3, p. 195; Arch. f. path. Anat. u. Physiol. **6**:525, 1854.

7. Tauber, R.: Monatsschr. f. Geburtsch. u. Gynäk. **71**:95, 1925.

8. Erede, U.: Arch. di biol. **5**:29, 1928.

9. Johns, J.: J. Michigan M. Soc. **32**:504, 1933.

10. Tuta, J. A.: Arch. Path. **33**:78, 1942.

10a. Mandelstamm, A.: Monatsschr. f. Geburtsch. u. Gynäk. **83**:69, 1929.

10b. Gupta, N.: Indian M. Gaz. **66**:379, 1931.

11. Ehnmark, E.: Upsala läkaref. förh. **34**:219, 1928.

The first reported true uterine angioma was described by Klob,[12] who called it cavernous ectasia of the uterus. It was located on the posterior wall of the uterine cavity of an elderly woman and was a bluish red elevated tumor measuring 2 cm. in diameter. Klob expressed the belief that this tumor resulted from failure of the placental site to undergo involution synchronously with the rest of the uterus.

The second uterine angioma occurred in a 37 year old nullipara and was described by Boldt [13] as an oval tumor found in one uterine horn and measuring 4 by 2 by 2 cm. Since this tumor developed despite the absence of previous pregnancies Boldt felt that uterine angioma was not related etiologically to poor involution of the placental site.

A third angioma of the uterus was a 6 cm. polypoid soft tumor with an irregular, knoblike surface, found by Boks [14] in the anterior wall of the uterus of a 37 year old multipara.

In 1923 Meyer [15a] stated that angioma of the uterus was rare and that he had seen only 1 case in which he believed it had occurred in an area of old granulation tissue. The growth was discovered in the curettings of a 62 year old woman. In 1925 Meyer [15b] presented 4 additional cases of telangiectasis of the uterus. He described the findings as being circumscribed, irregularly shaped, blood red tumors in the inner portion of the myometrium. Two of them extended into the mucosa, and the largest of the 4 tumors measured 4 mm. in diameter.

Neumann [16a] contributed two papers on the subject, the first of which concerned a 38 year old woman who had been pregnant, three times but had given birth to no children. A submucous polypoid mass was found filling the entire uterine cavity and measuring 10 by 7 by 7 cm., with large vacuoles visible on the surface of the tumor, which microscopically was characterized by large conglomerations of blood vessels of varying caliber, both arteries and veins. In his second paper Neumann [16b] reported 2 cases in which small telangiectatic spots were found in uteri with myoma, but not intimately associated with it, one being immediately under the serosa and the other immediately under the mucosa.

Horgan [17] recorded the case of a 46 year old multipara whose uterus was twice the normal size. In the anterior wall there was a tumor measuring 5 cm. in diameter, with dark red and purplish lobules bulging into the peritoneal and uterine cavities. Microscopic sections revealed numerous large spaces lined by a thin layer of endothelium and supported by a connective tissue framework.

12. Klob, J. M.: Pathologische Anatomie der weiblichen Sexualorgane, Vienna, Wilhelm Braumüller, 1864, p. 173; translated by J. Kammerer and B. F. Dawson, New York, Moorhead, Simpson & Bond, 1868, p. 183.

13. Boldt, H. J.: Am. J. Obst. & Gynec. **28**:834, 1893.

14. Boks, D. B.: Nederl. tijdschr. v. geneesk. **53**:694, 1917.

15. Meyer, R.: (*a*) Ztschr. f. Geburtsch. u. Gynäk. **87**:653, 1924; (*b*) Arch. f. Gynäk. **126**:609, 1925.

16. Neumann, H. O.: (*a*) Arch. f. Gynäk. **131**:50, 1927; (*b*) **139**:161, 1929.

17. Horgan, E.: Surg., Gynec. & Obst. **50**:990, 1930.

Bartsch [18] reported a hemangioma found in the uterus of a 53 year old multipara. It was a 2 by 1.5 by 1.5 mm. submucous mass which on section was characterized by a system of endothelium-lined spaces partly filled with fresh blood and partly with hyalinized thrombi.

Ratzenhofer [19] reported a 46 year old woman who began to experience episodes of excessive bleeding at the age of 19 after a normal termination of her only pregnancy. These continued to occur with little relief through the years, and occasionally there was a sharp hemorrhage. The only gross abnormality of the uterus noted was a red discoloration of the inner layers of the myometrium. Microscopically the outer half of the myometrium was normal, but the inner half contained numerous small and medium-sized endothelium-lined spaces with thin walls, filled with blood. The lesion was diagnosed as angiomatosum uteri. Since there were no associated conditions or nutritional demands to account for the new growth of vessels, this would seem to be more properly termed hemangioma of the uterus.

Roentgen hysterography revealed a tumor in the left horn of the uterus of a 40 year old woman who had been pregnant twice but had given birth to no children. After removal of the uterus and microscopic examination of the tumor, it was reported as angioma of the uterus by Lévy-Solal, Bret and Duperrat.[20]

To recapitulate briefly, 15 cases appear to fall under the classification of angioma of the uterus. In 3 cases, reported by Klob,[12] Boldt [13] and Boks,[14] respectively, the tumors varied from 2 to 4 cm. in size. In 5 cases reported by Meyer [15] all the tumors were under 4 mm. in size; 4 lay in the myometrium and 1 in the endometrium. Neumann [16] reported 1 large polypoid hemangioma of the uterus and 2 other small telangiectatic uterine tumors. Finally, in recent years Horgan,[17] Bartsch,[18] Ratzenhofer [19] and Lévy-Solal and associates [20] recorded 1 case each.

COMMENT

The diagnosis of uterine angioma is essentially a pathologic one, there being no reasonable clinical grounds for reaching such a diagnosis. A localized new growth of endothelium-lined vessels in a uterus with normal structure, where there is neither venous stasis nor unusual nutritional demands, and not in intimate association with fibromyoma, should be recognized as angioma. If the vessels contain blood cells not present as a result of local hemorrhage, it may be termed "hemangioma." The term "lymphangioma" is reserved for the vascular tumors which arise from lymph vessels and which consequently are not expected to contain blood cells. Those vascular tumors which show invasive characteristics are best classified with endothelioma.

In discussing these vascular neoplasms designated as uterine angioma several authors have advanced the thought that this type of tumor may be the result of faulty involution of a pregnant uterus, possibly beginning as a small retained placental fragment. This seems

18. Bartsch, G. H.: Zentralbl. f. Gynäk. **54**:3138, 1930.

19. Ratzenhofer, M.: Wien. klin. Wchnschr. **53**:874, 1940.

20. Lévy-Solal, E.; Bret, J., and Duperrat, B.: Gynéc. et obst. **44**:332, 1944-1945.

fallacious for several reasons. It presupposes that uterine angioma is etiologically different from angioma found in other parts of the body. It fails to account for the vascular tumor found by Boldt in a uterus that had never been pregnant. Finally, it neglects to account for the few times angioma has been encountered in the many multigravid uteri examined pathologically. Indeed, the extreme infrequency of the finding of uterine angioma in the presence of such seemingly favorable conditions as are found in the uterus would lend credence to the general belief that angioma either is congenital or develops early in life.

SUMMARY

A case of submucous polypoid hemangioma is added to the 15 previously reported cases of angioma of the uterus, and the literature is briefly reviewed.

Books Received

JORDAN-BURROWS TEXTBOOK OF BACTERIOLOGY. By William Burrows, Ph.D., professor of bacteriology, department of bacteriology and parasitology, University of Chicago. Fifteenth edition. Cloth. Pp. 981, with 264 illustrations. Price $9. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1949.

This, the fifteenth edition of a standard and widely accepted textbook, is the first to have dropped the name of the late Dr. Jordan as the co-author, the sole authorship having been assumed by Dr. Burrows. He has attempted to keep pace with the rapid advances in the field of bacteriology. The section on chemotherapy and antibiotics has been considerably enlarged; there is a notable increase in emphasis on specific laboratory methods of diagnosis of bacterial diseases. Particularly praiseworthy are the many excellent new electron photomicrographs and a well integrated discussion on bacterial physiology. To some it may appear desirable, for the sake of uniformity in nomenclature, that the author should have adhered more closely to Bergey's classification (Aerobacter aerogenes rather than Bacterium aerogenes, etc.). The brief section on the helminths more properly belongs in a text on parasitology. There is no question in this reviewer's mind that the new edition will be as warmly received by students, clinicians and bacteriologists as were the fourteen preceding ones.

ISOTOPIC TRACERS AND NUCLEAR RADIATIONS WITH APPICATIONS TO BIOLOGY AND MEDICINE. By William E. Siri. With contributions by Ellsworth C. Dougherty, Cornelius A. Tobias, Rayburn W. Dunn, James S. Robertson and Patricia P. Weymouth, Division of Medical Physics, Department of Physics and Radiation Laboratory, University of California. Pp. 653, with 136 illustrations. Price $12.50. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 18, 1949.

The extensive tables, including the complete Seaborg and Perlman table of isotopes reprinted from *Review of Modern Physics* **20**:585, 1948) and the alphabetized reference list (according to elements and to authors under each element), which together cover approximately one fourth of the total pages, make this book the most practical handbook on isotopes published to date. For these reasons alone the book is of considerable value to the pathologist and to others interested in the practical application of isotopes in their own studies in biologic and medical research. To get the utmost benefit from this book, it is necessary that the reader have some knowledge of calculus.

The book is divided into three sections. The first section is primarily concerned with the properties of nuclear radiations, and it is in this section that the extensive tables are included. The physical principles set down and the data presented come from literature scattered in many physical science publications. To the reviewer's knowledge such a complete compilation has not appeared elsewhere.

The second section on methods and instruments presents, with the aid of figures and schematic circuit drawings, the essentials in theory, construction and practical significance of all methods of producing nuclear radiations, of means of their detection, and of many ways of handling them safely.

The third section, written by Dr. Ellsworth C. Dougherty, on biologic and medical applications is presented "in the form of a survey of those isotopes which have already been used and those which, because of their convenient physical properties and biologic significance, may reasonably be employed in future research."

This section is not a detailed account of medical and biologic research. Rather, it is concerned with the variety of ways in which these new tools may be applied to medical research, i. e., the isotopes best suited for the study of the major organic metabolites, those best suited for the study of the major mineral metabolites, those for use in common pharmacologic and toxicologic studies, and those most valuable in therapeutic and diagnostic procedures.

EXTERNAL MORPHOLOGY OF THE PRIMATE BRAIN. By Cornelius J. Connolly, Ph.D., professor of physical anthropology, Catholic University of America, Washington, D. C. Pp. 386, with 343 illustrations and 16 tables. Price $10. Charles C Thomas, 307-327 East Lawrence Ave., Springfield, Ill., 1950.

This book is a scholarly comparative account of the fissuration of the primate brain. The author has had long experience in this field and has spared no effort to complete his documentation. His studies are reported with sober scientific accuracy, and the result is a standard reference on the subject which takes into account not only the extensive material available to the author but also all the vast pertinent literature.

According to a standardized method, the sulci are described, first of the lower and intermediate primates—Lemuroidea, Tarsioidea, Anthropoidea platyrrhini and catarrhini—then of the anthropoids—gibbon, orang-utan, chimpanzee and gorilla.

In the chapter on encephalometry, the author states that there is no generally accepted method of measuring the brain. He insists on the necessity that the brain be fixed before removal, and gives his own procedure for measuring. He has modified the Schwartz stereograph so as to be able to use most of the operations carried out with the stereograph on the cranium. He portrays the instrument and explains its use.

After describing in a brief chapter the manner in which the cerebral sulci develop in the human fetus, the author proceeds to an account of the brain of the newborn infant and the child.

The careful and detailed account of the adult human brain is based on study of the brains of 30 white persons and 30 Negroes. The author comes to the conclusion that no morphologic feature is found to be exclusively characteristic either of the white person's or of the Negro's brain, so that no feature enables one to tell the racial provenience of any individual brain. There seems to be some difference of frequency of certain features, especially in the occipital lobe.

Although the author rightly states that there is no general consensus concerning the possibility that there is a relationship between sulci and cytoarchitectonic areas, this is not true respecting the lunate sulcus, which always develops just anterior to the anterolateral margin of the striate area. Most of the studies on the lunate sulcus of the human brain are worthless because of lack of microscopic verification. Unless a suspected sulcus bears this characteristic relationship to the striate area, it is not the lunate. Using this criterion, the reviewer has never found a lunate sulcus in the brain of either a white person or a Negro.

The long discussion of endocranial casts and the conclusions one may draw from them are doubtless interesting and important to anthropologists, but the pathologist will find here little of use to him.

The author concludes that the sulci originate from intrinsic factors, although mechanical factors acting on the surface of the brain may modify their form and position. The position of the major sulci and their topographic relations are quite constant throughout the primate series.

This scholarly and beautifully printed book will be invaluable to everyone interested in the study of the brain.

ELECTROCARDIOGRAPHY, FUNDAMENTALS AND CLINICAL APPLICATION. By Louis Wolff, M.D., visiting physician, consultant in cardiology and chief of the electrocardiographic laboratory at Beth Israel Hospital and associate in medicine at Harvard Medical School. Pp. 187, with 110 figures. Price $4.50. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftsbury Ave., London W.C.2, 1950.

QUESTIONS, MEDICAL STATE BOARD AND ANSWERS (NEW, 8TH EDITION). By R. Max Goepp, M.D., formerly professor of clinical medicine at the University of Pennsylvania Graduate School and professor of medicine at Woman's Medical College of Pennsylvania; and Harrison F. Flippin, M.D., associate professor of Medicine at the University of Pennsylvania Graduate School. Pp. 663. Price $7. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftsbury Ave., London W.C.2, 1950.

L'ORGANISATION DES OS. By Pierre Lacroix, professor at the University of Louvain, Belgium. Paper bound. Pp. 230, with 87 figures. Price 900 francs. Masson & Cie, 120 Boulevard Saint-Germain, Paris 6e, France.

PATHOLOGY OF THE NERVOUS SYSTEM: A STUDENT'S INTRODUCTION. By J. Henry Biggart, M.D., C.B.E., D. Sc., professor of pathology at Queen's University, Belfast; pathologist to the Royal Victoria Hospital, Belfast Hospital for Sick Children, Claremont Street Hospital for Nervous Diseases and Mater Infirmorum Hospital. Foreword by Prof. A. Murray Drennan, M.D., F.R.C.P.E., F.R.S.E. Second edition. Pp. 352, with 232 illustrations and 10 colored plates. Price $6. Williams and Wilkins Company, Mt. Royal & Guilford Aves., Baltimore 2, 1949.

This revised edition remains one of the best introductions to the study of the pathology of diseases of the nervous system. As such it is of particular use to medical students, as intended by the author. Not burdened by extraneous detail, it offers a concise and lucid presentation of neuropathologic conditions from the point of view of the general pathologist. The approach to and classification of diseases are along etiologic lines whenever possible, and the author is thus able to present his material in fourteen well differentiated chapters. There are about forty new illustrations. These, with some replacement of previous reproductions, are of high quality.

DARMBRAND: ENTERITIS NECROTICANS (INTESTINAL GANGRENE OR NECROTIC ENTERITIS). By K. Hansen, E. Jeckeln, J. Jochims, A. Lezius, H. Meyer-Burgdorff, and F. Schütz. Städtische Krankenanstalten Lübeck. Price $7.50; 25 marks. Pp. 121, with 103 illustrations. Georg Thieme, Diemershaldenstrasse 47, Stuttgart-O, Germany, 1949.

During the summer of 1946 a hitherto unrecognized form of enteric disease made its appearance in Northern Germany. It grew to epidemic proportions in 1947. This monograph records the pathologic observations, the clinical course and the experimental observations. All age groups were affected. In the very young and the old the disease was particularly severe and the mortality high. Males were oftener affected than females. The disease was characterized by a triad of symptoms, viz., abdominal pain, diarrhea and disturbances in nutrition. The clinical course was peracute, acute or subacute, with or without sequelae. The small intestine was the chief seat of the disease, which oftener involved its proximal than its distal portions. Necrotic patches, primarily in the intestinal folds but subsequently becoming more confluent, extended from the mucosa to variable depths,

down to the serosa at times. The deeper lying, non-necrotic portions of the bowel were markedly edematous and hyperemic, with often thrombosed and necrotic blood vessels. There was, however, little cellular exudate. The processes of repair were associated with the formation of granulation tissue beneath the necrotic layers, with subsequent separation of the latter, leading either to superficial flat scars or to frank stenosing lesions. Adynamic ileus with or without perforation was seen early. In late stages, mechanical obstruction as a result of stenoses with or without perforation was again observed. Bacteriologic and experimental studies point toward Bacillus welchii, type F, as being the causal agent and toward the pathogenetic importance of its beta toxin.

CLINICAL DIAGNOSIS BY LABORATORY EXAMINATIONS. By John A. Kolmer, M.S., M.D., Dr. P.H., professor of medicine in the Temple University School of Medicine and School of Dentistry, Philadelphia. Second edition. Cloth. Price $12. Pp. 1,236 with 93 illustrations. D. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York, 1949.

In the present edition this work has been thoroughly revised and brought up to date. Much new material has been included in all the sections of the book. In spite of the additions, which include 18 figures, the total number of pages remains about the same.

The presentation and the organization of subject matter have not changed significantly. The work is divided into three parts. The first includes the clinical interpretations of practically all the tests used in the laboratory. A most valuable feature is the tables summarizing the contents of each chapter in concise wording.

The second part is devoted to the practical application of laboratory examinations and covers a large number of diseases, such as those of the blood, the urinary, digestive and cardiovascular systems, the respiratory tract, metabolism, venereal diseases, infectious diseases, vitamin deficiencies and disturbances of endocrine glands.

The third part deals with technics of laboratory tests, which are concisely presented.

During the six years since the book was first published it has gained well deserved popularity as the standard text on the interpretation of laboratory examinations. The thoroughness of the revision and the many corrections and improvements guarantee that the monograph will retain its old adherents and gain new ones. The 139 diagnostic summarizing tables alone make the book valuable to the student and the teacher. The excellent organization of the index (there are 108 pages of it) helps in finding the necessary specific information rapidly. The references at the end of each chapter have been brought up to date. Paper, print and binding continue to be pleasing.

This is a volume for every physician, regardless of specialty—for the clinical pathologist as well as the rest.

NEOPLASMS OF THE DOG. By R. M. Mulligan, M.D., professor of pathology in the University of Colorado Medical Center School of Medicine. Pp. 146, with 194 illustrations on 59 plates. Price $4. Williams & Wilkins Company, Mt. Royal & Guilford Aves., Baltimore 2, Md.

This book presents a compendium of information about canine tumors principally for the benefit of veterinarians, although the classifications and the wealth of histopathologic detail are of interest to the pathologist dealing with human and experimental cancer. Drawing from his considerable experience the author gives statistical data relative to the incidence of types of tumors among the many breeds of dogs and outlines the biologic properties of these tumors. At the conclusion of

the volume he deals briefly with technical methods of tissue preparation. Numerous photomicrographs and illustrations of gross specimens excellently supplement the text.

DIAGNOSTIK DER KREISLAUFFRÜHSCHÄDEN: PHYSIOLOGISCHE SCHWANKUNGSBREITEN, REGULATIONSSTÖRUNGEN UND BEGINNENDE SCHÄDEN DES KREISLAUFES. By Prof. Dr. Herbert Reindell, archiater of medicine, University Clinic, Freiburg i. Br. Price 44.40 deutschmarks. Pp. 518, with 161 illustrations and 4 tables. Ferdinand Enke Verlag, Hasenbergsteige 3, Stuttgart, 1949.

MICROBIOLOGY. By Florence C. Kelly, Ph.D., and K. Eileen Hite, M.D., Ph.D. Pp. 592, with 185 illustrations and 22 tables. Price $6.50. Appleton Century-Croft, Inc., 35 W. 32d St., New York (34 Bedford St., Strand, London W. C. 2), 1949.

This book is divided into eight parts headed respectively (1) "Introduction to the Microscopic World," (2) "Methods of Studying Micro-organisms," (3) "Physiology of Bacteria," (4) "Microbial Populations," (5) "Antimicrobial Methods," (6) "Micro-organisms and Disease," (7) "Pathogenic Microbiology" and (8) "Epidemiology and Public Health." Each one of these parts is divided into various chapters and the chapters contain numerous illustrations. Since the text is chiefly concerned with medical microbiology, especially pathogenic bacteria, the title may be somewhat misleading, although 92 pages are devoted to a brief presentation of virus diseases, pathogenic fungi and protozoa of medical importance. The book has an appendix giving the early milestones of microbiology and a section on technical methods of bacteriology which should prove useful for the beginning student. Key references are given for each chapter at the end of the book.

The reviewer regards it as a good text for the teaching of elementary courses in medical microbiology, especially suited to students interested in the medical sciences. It should prove useful for students engaged in the allied disciplines of pharmacy, dentistry or public health nursing, especially where the laboratory work of the teaching department is already adapted to such standard works as Zinsser's "Textbook of Bacteriology," since in approach and treatment of the subject it closely parallels the latter text.

HUMAN PATHOLOGY. By Howard T. Karsner, M.D., LL.D., former professor of pathology, Western Reserve University; medical research adviser to the Bureau of Medicine and Surgery, United States Navy. Seventh edition. Pp. 927, with 562 illustrations in black and white and 22 subjects in color on 14 plates. Price $12. J. B. Lippincott Company, 227-231 South Sixth Street, Philadelphia; Durham House, 16 John St., Adelphi, London, W.C.2. 1949.

Notes and News

Deaths.—Orin Author Ogilvie, founder and director of the Wasatch Laboratories and for many years a member of the faculty of the University of Utah School of Medicine, died Nov. 8, 1949, aged 54, in Salt Lake City. He was a specialist certified by the American Board of Pathology; a member of the College of American Pathologists and the American Society of Clinical Pathologists, and a former president of the Utah State Medical Association and the Salt Lake County Medical Society.

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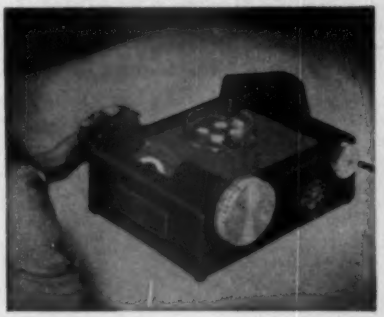

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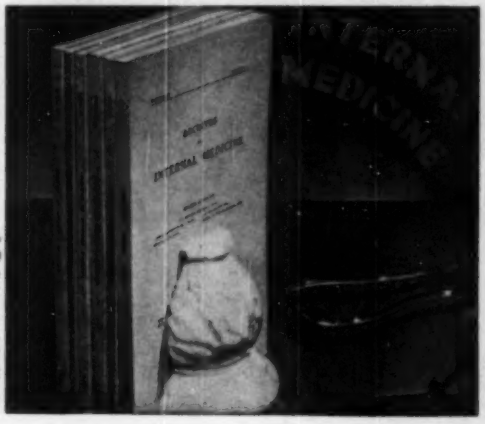

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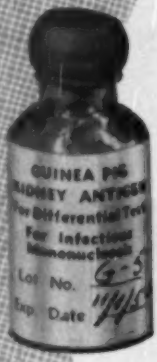

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1. I. DAVIDSOHN, K. STERN and CHIYO KASHIWAGI: The Differential Test for Infectious Mononucleosis; Abraham Levinsohn Anniversary Volume Studies in Pediatrics and Medical History, Froben Press, Inc., New York 1949.

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